Pseudoephenamine: A Practical Chiral Auixiliary for Asymmetric Synthesis

Dissertation Advisor: Professor Andrew G. Myers Marvin Rocael Morales Santos

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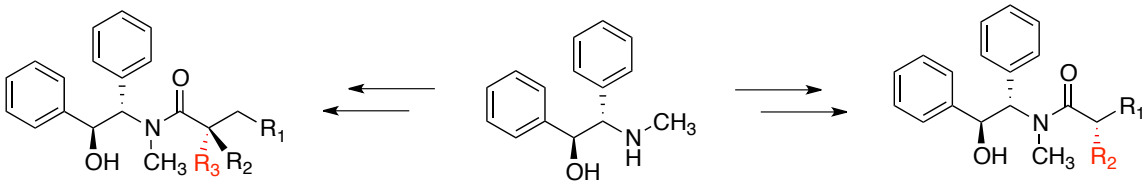
Abstract

Pseudoephedrine has been used as a chiral auxiliary in diastereoselective alkylation reactions, providing easy access to enantiomerically enriched carboxylic acids, alcohols, ketones, and aldehydes. Because pseudoephedrine can be transformed into methamphetamine and other illegal drugs, many countries restrict or ban its sale and distribution, which can complicate its use in academic and industrial settings. This thesis shows that (1*S*,2*S*)-2-methylamino-1,2-diphenylethanol and (1*R*,2*R*)-2-methylamino-1,2-diphenylethanol (synonymously, (1*S*,2*S*)- and (1*R*,2*R*)-pseudoephenamine **30**, respectively) enable a broad range of utilities in asymmetric synthesis that meet or exceed those that previously characterized the pseudoephedrine system alone, with several advantages. First, these auxiliaries are free from regulatory restrictions and are not known to be transformable into illegal substances; second, asymmetric alkylation reactions that employ pseudoephenamine as a chiral auxiliary proceed with equal or greater diastereoselectivities than the corresponding reactions employing pseudoephedrine, with notable improvements in the selectivities of the alkylation reactions that form quaternary carbon stereocenters; and lastly, amides derived from pseudoephenamine exhibit a greater propensity to be crystalline compounds than the corresponding pseudoephedrine derivatives.



75 – 91% yield

19:1 dr

30

(–)-pseudoephenamine

84 – 99% yield

98:2 to ≥99:1 dr

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Para mis padres:

Jose e Irma Morales

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ABBREVIATIONS

Å	angstrom
Bn	benzyl
c	concentration (g/100 mL)
CAM	aqueous ceric ammonium molybdate solution
cis	*L.*, on the same side
DMPU	1,3-dimethyl3,4,5,6-tetrahydro-2(1*H*)-pyrimidinone
dr	diastereomeric ratio
E	*Ger.*, entgegen
ee	enantiomeric excess
ent	enantiomer
equiv	equivalent
ESI	electrospray ionization
Et	ethyl
FTIR	Fourier transform infrared
g	gram
HPLC	high-performance (pressure) liquid chromatography
HRMS	high-resolution mass spectrometry
Hz	hertz
J	coupling constant (in Hz)
KHMDS	potassium hexamethyldisilazide
LDA	lithium diisopropylamide
M	molar (mol/liter)

mg	milligram
MHz	megahertz
mL	milliliter
mmol	millimole
NBS	*N*-bromosuccinimide
Ni	nickel
NMR	nuclear magnetic resonance
nOe	nuclear Overhauser effect
Pd	palladium
Ph	phenyl
ppm	parts per million
Pt	platinum
R	rectus (Cahn-Ingold-Prelog system)
Red-Al	sodium bis(2-methoxyethoxy)aluminum hydride
R_f	retention factor
Rh	rhodium
Ru	ruthenium
S	sinister (Cahn-Ingold-Prelog system)
TCA	trichloroacetic acid
Tf_2O	trifluoromethanesulfonic anhydride
TFA	trifluoroacetic acid
THF	tetrahydrofuran
TLC	thin-layer chromatography

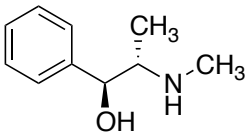
trans	*L.*, across
UV	ultraviolet
Z	*Ger.*, zusammen

Chapter 1

Introduction to Pseudoephedrine Chemistry

Introduction

Pseudoephedrine **1** is a commodity chemical that has been produced in excess of 300 metric tons per year. It has been sold as an over-the-counter medication (Sudafed®, Claritin-D®, etc.) in many countries until the mid-2000s. Pseudoephedrine is an amino alcohol that is used as a chiral auxiliary for asymmetric alkylation reactions. In the mid-1990s, Myers and co-workers published the use of pseudoephedrine as a practical chiral auxiliary for the synthesis of enantiomerically enriched carboxylic acids, aldehydes, alcohols, and ketones.[1]



1

(+)-(1*S*,2*S*)-pseudoephedrine

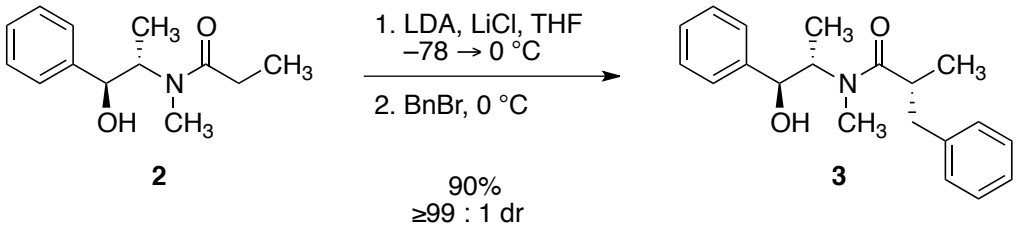
Figure 1.1 Structure of (+)-(1*S*,2*S*)-pseudoephedrine.

Alkylation of Pseudoephedrine Amides

Pseudoephedrine amides enolates are alkylated in high yields and high diastereoselectivities with a variety of alkyl halides. Typically, pseudoephedrine amides are deprotonated with lithium diisopropylamide (LDA, 2.25 equiv) in the presence of

[1] (a) Myers, A. G.; Yang, B. H.; Chen, H.; Gleason, J. L. *J. Am. Chem. Soc.* **1994**, *116*, 9361-9362. (b) Myers, A. G.; Yang, B. H.; Chen, H.; McKinstry, L.; Kopecky, D. J.; Gleason, J. L. *J. Am. Chem. Soc.* **1997**, *119*, 6496-6511. (c) Myers, A. G.; Gleason, J. L.; Yoon, T. *J. Am. Chem. Soc.* **1995**, *117*, 8488-8489. (d) Myers, A. G.; Yoon, T.; Gleason, J. L.; *Tetrahedron Lett.* **1995**, *36*, 4555-4558. (e) Myers, A. G.; Yoon, T. *Tetrahedron Lett.* **1995**, *36*, 9429-9432. (f) Myers, A. G.; Gleason, J. L.; Yoon, T.; Kung, D. W. *J. Am. Chem. Soc.* **1997**, *119*, 656-673. (g) Myers, A. G.; McKinstry, L.; Gleason, J. L. *Tetrahedron Lett.* **1997**, *38*, 7037-7040. (h) Myers, A. G.; McKinstry, L.; Barbay, J. K.; Gleason, J. L. *Tetrahedron Lett.* **1998**, *39*, 1335-1338. (i) Myers, A. G.; Barbar, J. K.; Zhong, B. *J. Am. Chem. Soc.* **2001**, *123*, 7207-7219. (j) Myers, A. G.; McKinstry, L. *J. Org. Chem.* **1996**, *61*, 2428-2440.

lithium chloride (6 equiv) in tetrahydrofuran (THF). The resulting dianion is then alkylated with alkyl halides (1.5–4.0 equiv) at 0 ºC or –78 ºC affording the tertiary alkylation product. The crystallinity of some of the products allows one to isolate the major diastereomer with ≥ 99 : 1 dr by recrystallization (Scheme 1.1).



Scheme 1.1 An example of a pseudoephedrine amide alkylation (benzylation of pseudoephedrine propionamide).

An extension of this methodology to construct quaternary carbon-center products derived from α,α-disubstituted pseudoephedrine amides was achieved in 2008.[2] We reported two methods for the stereocontrolled construction of quaternary carbon centers. The first method is sequential enolization-alkylation of pseudoephedrine amides. With this method, it was found that by using excess enolate (>1.25 equiv) the desired product was obtained with higher diastereoselectivities and with shorter reaction times than by using limiting enolate and excess electrophile. Typically, tertiary amide products are deprotonated with LDA in the presence of lithium chloride (6 equiv) at 0 ºC for 3 h,

[2] Kummer, D. A.; Chain, W. B.; Morales, M. R.; Quiroga, O.; Myers, A. G. *J. Am. Chem. Soc.* **2008**, *130*, 13231-13233.

followed by addition of 1,3-dimethyl-3,4,5,6-tetrahydro-2(1*H*)-pyrimidinone (DMPU, 2.5 equiv) and then alkyl halide (1 equiv) at –40 ºC. The products are isolated in good yields (78–99%) and good to moderate diasteroselectivities (5.4 – ≥19:1 dr), Chart 1.1.

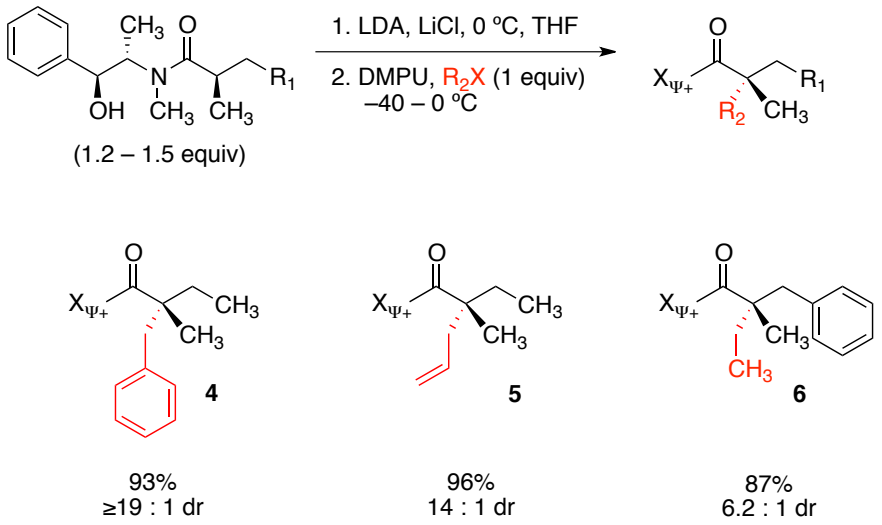


Chart 1.1 Formation of quaternary carbon centers by enolization-alkylation of α,α-disubstituted pseudoephedrine amides.

The second method is conjugate addition-alkylation of α-alkyl-α,β-unsaturated pseudoephedrine amides.[3] Typically, the benzylic hydroxyl group of the acrylamides is deprotonated with methyllithium (1.05 equiv) in the presence of lithium chloride (6 equiv) at –78 ºC in tetrahydrofuran. Conjugate addition of an organolithium reagent (1.2 equiv) led to enolate formation, which was subsequently treated with alkyl halides (≥2 equiv) to yield the desired quaternary products in good yields (72–99%) and good to

[3] (a) Reyes, E.; Vicario, J. L.; Carrillo, L.; Badia, D.; Iza, A.; Uria, U. *Org. Lett.* **2006**, *8*, 2535-2538. (b) Reyes, E.; Vicario, J. L.; Carrillo, L.; Badia, D.; Uria, U.: Iza, A. *J. Org. Chem.* **2006**, *71*, 7763-7772.

moderate diastereoselectivities (9.1 – ≥19:1 dr), Chart 1.2. In both of these cases, the quaternary carbon center products were oils, and separation of the diastereomers was not possible.

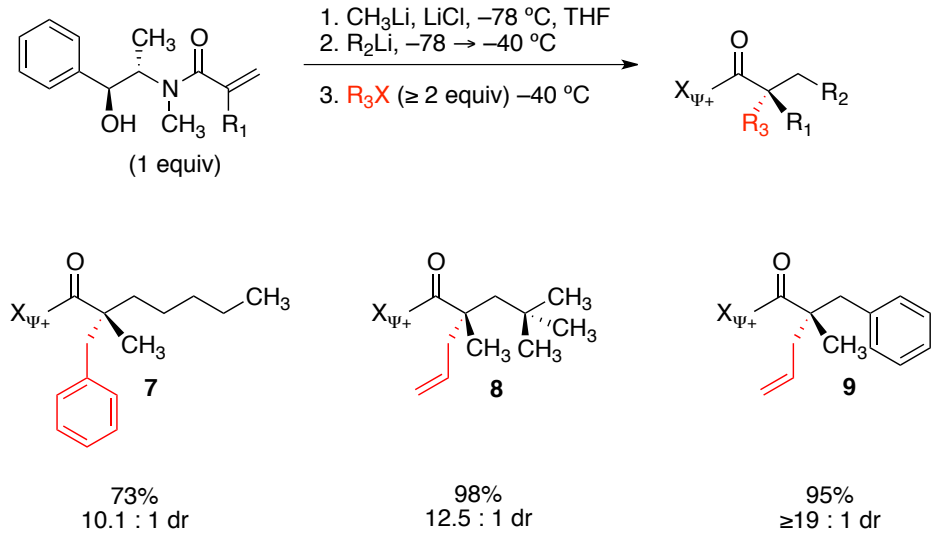


Chart 1.2 Formation of quaternary carbon centers by conjugate addition-alkylation of α-alkyl-α,β-unsaturated pseudoephedrine amides.

The reasoning for selectivity of pseudoephedrine amide enolate alkylations is based on limited experimental detail. Solution state structures of the enolate by NMR spectroscopy have been complicated due to line broadening and complex spectra. Attempts to obtain a solid-state structure of the enolate have been unsuccessful. A model of the reactive enolate conformation has been proposed, in which the pseudoephedrine backbone adopts a staggered conformation, positioning the lithium alkoxide and any solvent molecules (THF and diisopropylamine) above the plane defined by the N-C-O bond, blocking the β-face of the (*Z*)-enolate and forcing the alkylation to proceed from the α-face (Figure 1.2).[1b]

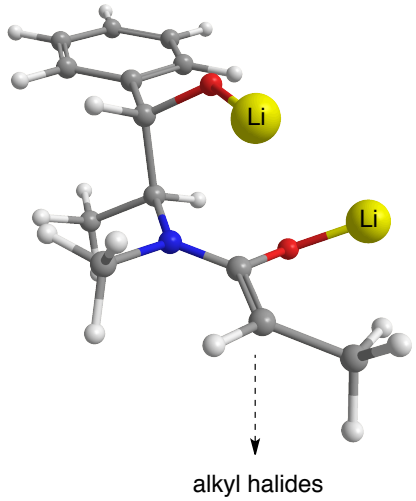


Figure 1.2 Proposed reactive conformation of pseudoephedrine amide enolates.

This model is supported by the X-ray crystal structure of pseudoephedrine glycinamide monohydrate (Figure 1.3).[1d] In this structure, both allylic and torsional strains are minimized, and the secondary alcohol and a bridging water molecule are positioned above the amide bond plane. Although this model accounts for the observed selectivity of pseudoephedrine amide enolates, some important aspects have been omitted: the ionization and aggregation states of the enolate, the rotamer distribution, and the degree of pyramidalization of the nitrogen.

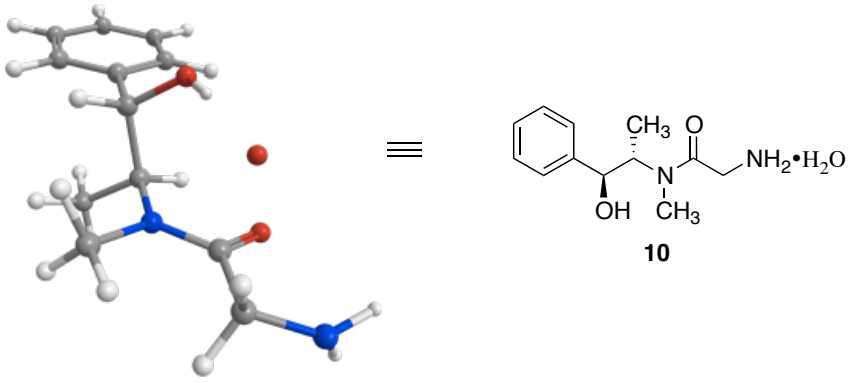
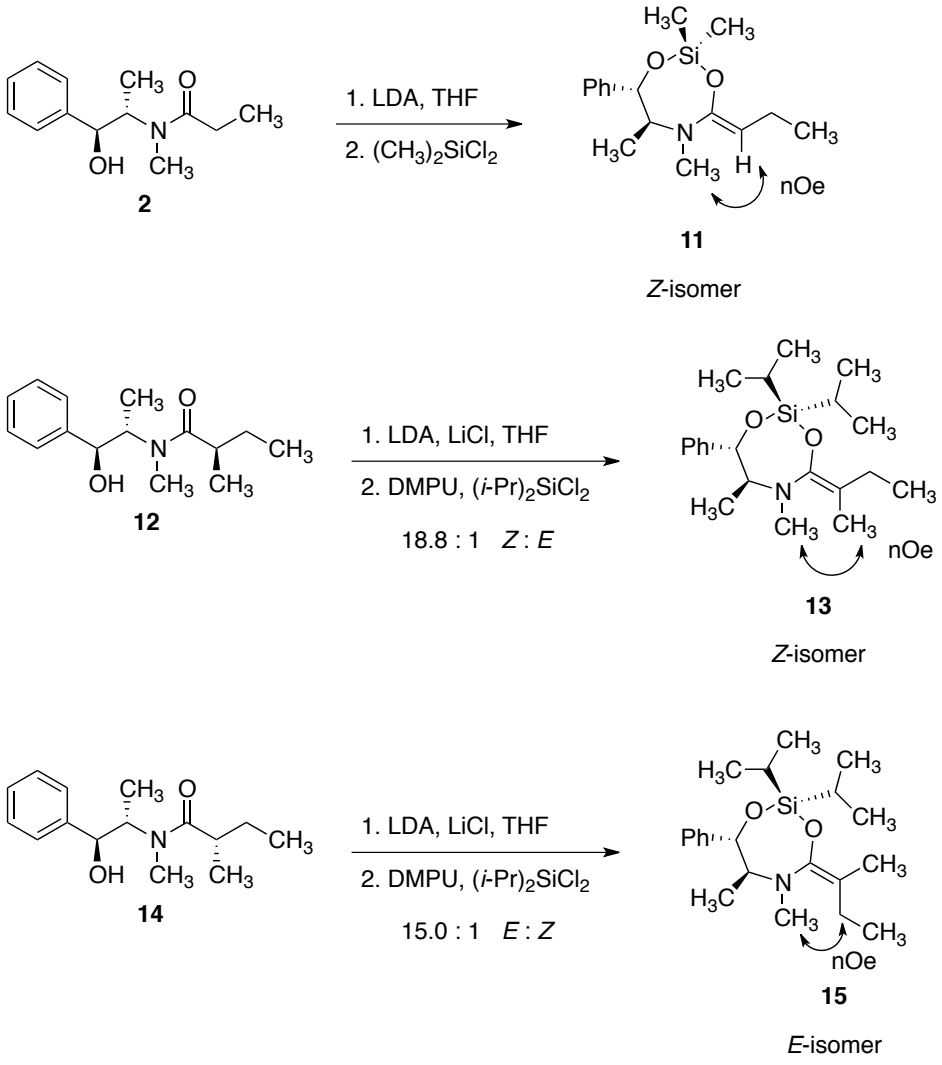


Figure 1.3 Crystal structure of pseudoephedrine glycinamide monohydrate.

Pseudoephedrine amide enolates have been trapped with dichlorodimethylsilane[4] or dichlorodiisopropylsilane[2] and the resulting silylketene *N*,*O*-acetals were evaluated by ^{1}H NMR, which shows which enolate isomer (*Z* or *E*) is favored upon deprotonation of the amide with LDA through nOe's between the *N*-methyl hydrogens and either the hydrogen or methylene hydrogens of the alkene substituent *cis* to the *N*-methyl group (Scheme 1.2). For example, in enolate **13**, the *Z*-isomer was found to be the major isomer through nOe's between the *N*-methyl hydrogens and the methyl group hydrogens of the alkene substituent *cis* to the *N*-methyl group.

[4] (a) Myers, A. G.; Widdowson, K. L.; Kukkola, P. J. *J. Am. Chem. Soc.* **1992**, *114*, 2765-2767. (b) Marsh, R. E.; Schaefer, W. P.; Widdowson, K. L.; Myers, A. G. *Acta. Cryst.* **1992**, *C48*, 1948-1951.



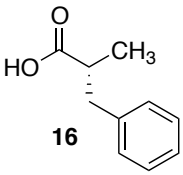
Scheme 1.2 Enolate trapping experiments.

Transformations of Pseudoephedrine Amides into Enantiomerically Enriched Carboxylic Acids, Ketones, Alcohols, and Aldehydes

Although the alkylation products are useful intermediates, their transformations into enantiomerically enriched carboxylic acids, ketones, alcohols, and aldehydes constitute a valuable addition to synthetic chemistry (for representative examples, see Chart 1.3).[1] Pseudoephedrine amides can be hydrolyzed using acidic (9 N or 18 N sulfuric acid, H_2SO_4, in dioxane) or basic (tetra-*n*-butylammonium hydroxide, *n*-Bu_4NOH, in a 3:1 mixture of *tert*-butyl alcohol and water) conditions. The resulting carboxylic acids are isolated in good yields and good enantioselectivities (87–97% yields, 88–97% ee). The auxiliary is recovered by a simple extractive workup. Pseudoephedrine amides can also be transformed into ketones by 1,2-addition of organolithium reagents. The ketones are isolated in good yields and high ee's (89–98% yield, ≥95% ee). Pseudoephedrine amides can be reduced to the corresponding primary alcohols by treatment with lithium amidotrihydroborate (LAB).[5] The alcohols are isolated in good yields and high ee's (83–90% yield, 92–99% ee). Pseudoephedrine amides can also be reduced to form aldehydes in a single step with lithium triethoxyaluminum hydride followed by treatment with trifluoroacetic acid. The aldehydes are isolated in good yields and high ee's (76–80% yield, 90–97% ee).

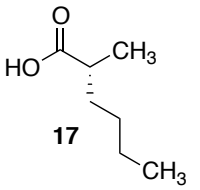
[5] (a) Myers, A. G.; Yang, B. H.; Kopecky, D. J. *Tetrahedron Lett.* **1996**, *37*, 3623-3626. (b) Myers, A. G.; Yang, B. H.; Chen, H. *Org. Synth.* **2000**, *77*, 29-44.

Carboxylic Acids (via acidic or basic hydrolysis):



16

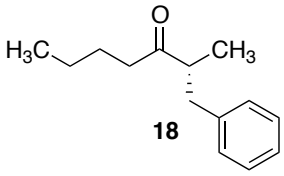
95%, 97% ee
93%, 94% ee



17

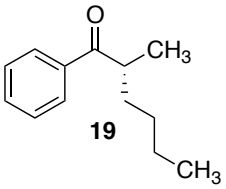
91%, 97% ee
93%, 97% ee

Ketones (via aryl or alkyllithium addition):



18

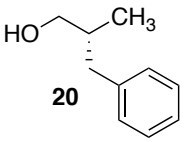
89%, ≥95%ee



19

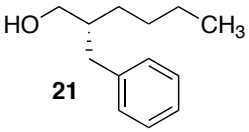
93%, ≥95% ee

Alcohols (via LAB reduction):



20

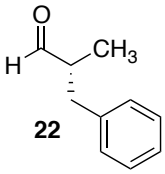
90%, ≥99% ee



21

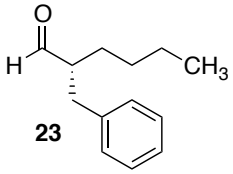
92%, ≥95% ee

Aldehydes (via $LiAlH(OEt)_3$ reduction):



22

76%, 95% ee

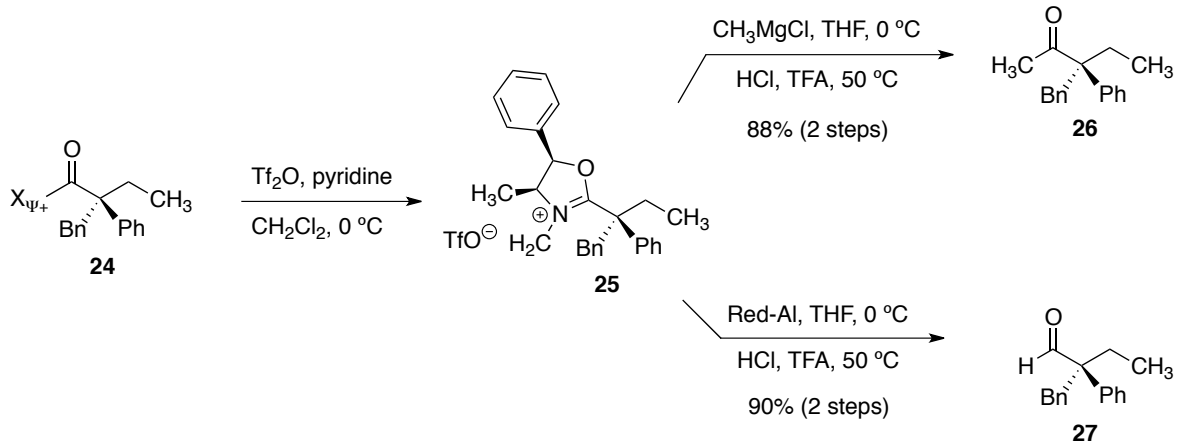


23

82%, 97% ee

Chart 1.3 Transformations of pseudoephedrine amides into enantiomerically enriched carboxylic acids, ketones, alcohols, and aldehydes.

The quaternary carbon center products can be transformed to aldehydes and ketones by a different reaction sequence.[2] First, the amide is treated with trifluoromethanesulfonic anhydride and pyridine to form a cyclic oxazolinium triflate **25**,[6] which is then treated with methyl magnesium chloride followed by acidic hydrolysis to afford the methyl ketone **26**; the cyclic oxazolinium triflate **25** can also be treated with bis(2-methoxyethoxy)aluminum hydride (Red-Al) followed by acidic hydrolysis to provide the aldehyde **27**.[7]



Scheme 1.3 Formation of methylketone **26** and aldehyde **27** via oxazolinium triflate.

[6] Chain, W. B.; Myers, A. G. *Org. Lett.* **2007**, *9*, 355-357.

[7] Examples of additions of Grignard reagents and Red-Al to oxazolinium ions: (a) Meyers, A. I.; Collington, E. W. *J. Am. Chem. Soc.* **1970**, *92*, 6676-6678. (b) Castro, A.; Ramirez, J.; Juarez, J.; Teran, J. L.; Orea, L.; Galindo, A.; Gnecco, D. *Heterocylces* **2007**, *71*, 2699-2708.

Liabilities and Need for New Auxiliary

During the past 10 years, the use of pseudoephedrine as a chiral auxiliary has been hindered by the increasing production and use of methamphetamine and other illegal drugs. Methamphetamine **28** is an illegal drug classified under Schedule II (limited therapeutic value) by the United Nations (UN) Convention on Psychotropic Substances.

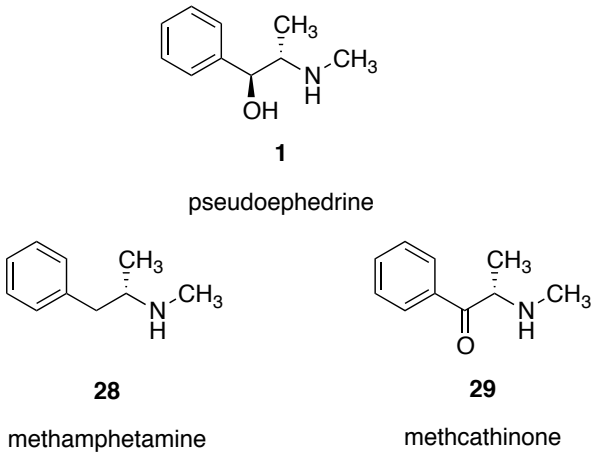
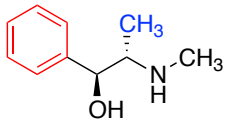


Figure 1.4 Structure comparison of pseudoephedrine, methamphetamine, and methcathinone.

Methcathinone **29** is an illegal drug classified under Schedule I (no therapeutic value) by the UN Convention on Psychotropic Substances. The reason that pseudoephedrine has been affected by these classifications is that one can make both drugs from pseudoephedrine; thus pseudoephedrine was placed in Table 1 (precursors to illegal drugs) of the UN Convention Against Illicit Traffic in Narcotic Drugs and Psychotropic Substances. Because of this, pseudoephedrine is highly regulated in many countries. The US requires government-issued identification (US passport/state identification card) to purchase pseudoephedrine; while Mexico, Colombia, and Japan prohibit the import and

export of pseudoephedrine. To overcome these limitations, our lab has sought to develop an alternative to pseudoephedrine that retains its use as a chiral auxiliary but lacks its liabilities. Specifically, the auxiliary should be free from regulatory restrictions; the asymmetric alkylation reactions should proceed with equal or greater diastereoselectivities than the corresponding reactions that employ pseudoephedrine; the amides derived from the new auxiliary should exhibit physical properties that facilitate their physical processing and spectroscopic analysis. I started this investigation by replacing the phenyl group of pseudoephedrine (in red, Figure 1.5) with other arene groups (e.g., 4-*tert*-butylphenyl, biphenyl, 1-naphthyl, and 2-naphthyl) with limited success; preliminary results from alkylation reactions were not promising. I then focused on the methyl group of the backbone (in blue, Figure 1.5) and found that substituting a phenyl group in that position did not change the diastereoselectivities of preliminary alkylation experiments. We found that (1*S*,2*S*)- and (1*R*,2*R*)-2-methylamino-1,2-diphenylethanol (pseudoephenamine **30**)[8] satisfies these criteria and, in most cases, is superior to pseudoephedrine as a chiral auxiliary.[9]



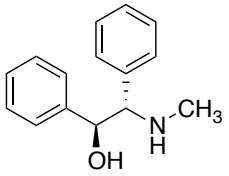
1

(+)-(1*S*,2*S*)-pseudoephedrine

Figure 1.5 Modification regions of (+)-(1*S*,2*S*)-pseudoephedrine.

[8] The term "ephenamine" was used in the Federal Registrat (June 7, 1951) to describe (*R*,*S*)-2-methylamino-1,2-diphenylethanol in a salt form of penicillin G, an antibiotic/feed additive used to stimulate growth in poultry and livestock.

[9] Morales, M. R.; Mellem, K. T.; Myers, A. G. *Angew. Chem. Int. Ed.* **2012**, *51*, 4568–4571.



30

pseudoephenamine

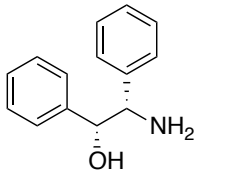
Figure 1.6 Structure of (–)-(1*S*,2*S*)-pseudoephenamine.

Chapter 2

Review of 1,2-diphenyl-2-aminoalcohols

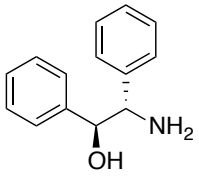
Introduction

This chapter will present a brief literature review of the following compounds: *erythro*-1,2-diphenyl-2-aminoethanol **31**, *threo*-1,2-diphenyl-2-aminoethanol **32**, ephenamine **33**, and pseudoephenamine **30**. The term "ephenamine" was used in the Federal Registrar (June 7, 1951) to describe (*R*,*S*)-2-methylamino-1,2-diphenylethanol in a salt form of penicillin G, an antibiotic/feed additive used to stimulate growth in poultry and livestock. We use the term "pseudoephenamine" to describe, (1*S*,2*S*)- and (1*R*,2*R*)-2-methylamino-1,2-diphenylethanol, the diastereomer of ephenamine.



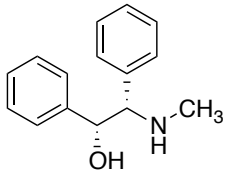
31

erythro-1,2-diphenyl-2-aminoethanol



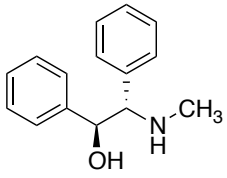
32

threo-1,2-diphenyl-2-aminoethanol



33

ephenamine



30

pseudoephenamine

Figure 2.1 Structures of related 1,2-diphenyl-2-aminoalcohols.

Synthesis and Use of *erythro*-1,2-diphenyl-2-aminoethanol and *threo*-1,2-diphenyl-2-aminoethanol

In 1887, Goldschmidt and Polonowska first described the synthesis of *erythro*-1,2-diphenyl-2-aminoethanol by reduction of benzoin oxime **34** with sodium amalgam (Scheme 2.1).[10] In 1899, Erlenmeyer reported that the *threo*-1,2-diphenyl-2-aminoethanol (isodiphenylethanolamine) derivative **37** was synthesized by the condensation of benzaldehyde and glycine; then, by heating **37** in the presence of tartaric acid, he was able to resolve *threo*-1,2-diphenyl-2-aminoethanol (Scheme 2.2).[11] This is the first reported synthesis of *threo*-1,2-diphenyl-2-aminoethanol, although the route has not been replicated, to our knowledge. In 1927, Read and Steele resolved *erythro*-1,2-diphenyl-2-aminoethanol by using *d*-oxymethylenecamphor and *d*-camphorsulfonic acid.[12]

In 1951, Tishler and co-workers at Merck reported a process for the large-scale synthesis (100 grams) of *erythro*-1,2-diphenyl-2-aminoethanol from the catalytic hydrogenation of benzoin oxime followed by resolution with glutamic acid (Scheme 2.3). They also reported the conversion of *erythro*-1,2-diphenylaminoethanol to *threo*-1,2-diphenyl-2-aminoethanol.[13] Both enantiomers of *erythro*-1,2-diphenyl-2-aminoethanol are commercially available ($550/100 g, Ace Synthesis LLC).

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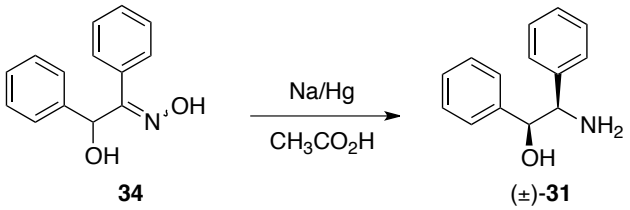
[10] (a) Goldschmidt, H.; Polonowska, N. *Chem. Ber.* **1887**, *20*, 492-495. (b) Soderbaum, H. G. *Chem. Ber.* **1895**, *28*, 2522-2524.

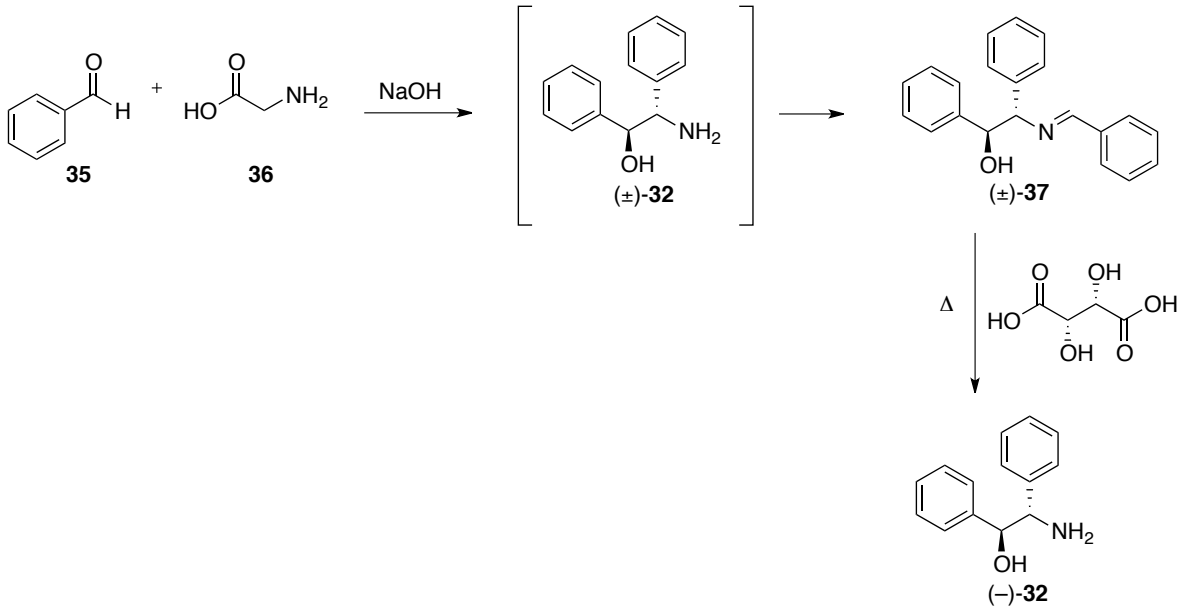
[11] (a) Erlenmeyer, E. *Annalen.* **1899**, *307*, 113-137. (b) Erlenmeyer, E. *Chem. Ber.* **1899**, *32*, 2377-2378. (c) Erlenmeyer, E. *Annalen.* **1904**, *337*, 307-328.

[12] Read, J.; Steele, C. C. *J. Chem. Soc.* **1927**, 910-918.

[13] Weijlard, J.; Pfister III, K.; Swanezy, E. F.; Robinson, C. A.; Tishler, M. *J. Am. Chem. Soc.* **1951**, *73*, 1216-1218.



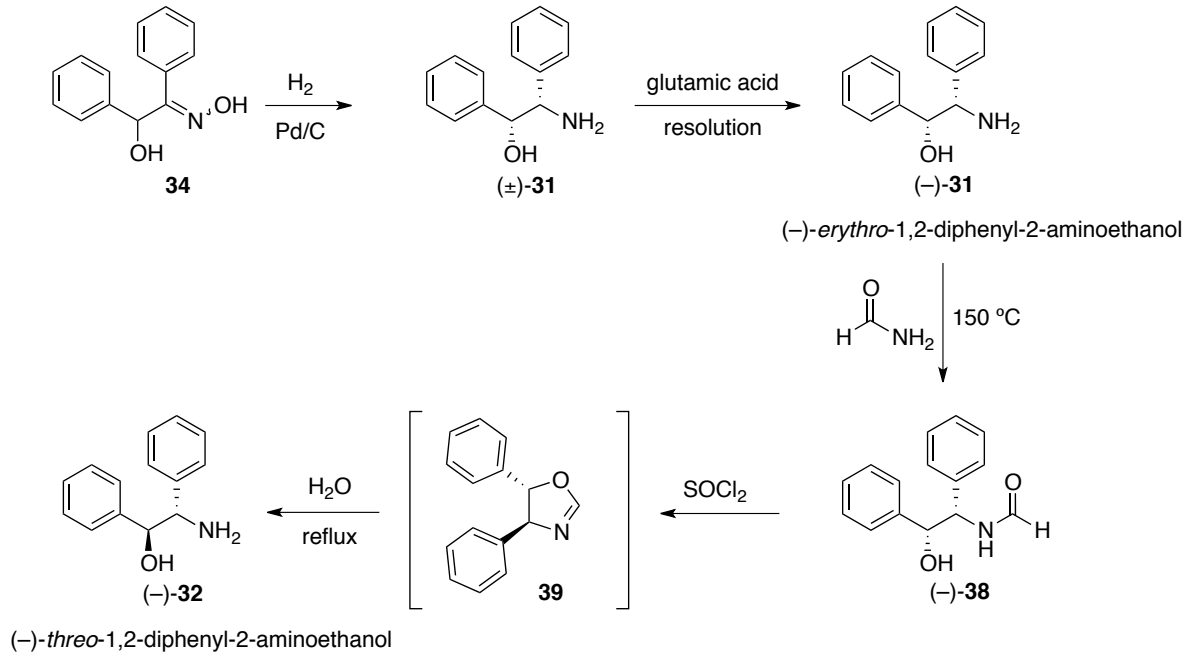
Scheme 2.1 Goldschmidt and Polonowska's synthesis of racemic *erythro*-1,2-diphenyl-2-aminoethanol.



Scheme 2.2 Erlenmeyer's synthesis and resolution of *threo*-1,2-diphenyl-2-aminoethanol.

The conversion of *erythro*-1,2-diphenyl-2-aminoethanol **31** to *threo*-1,2-diphenyl-2-aminoethanol **32** was achieved by *N*-formylation (**38**) with formamide, invertive cyclization to form the corresponding oxazoline **39** using thionyl chloride, followed by hydrolytic ring-opening under acidic conditions (Scheme 2.3).[13] The resulting solid was

recrystallized from hot ethanol. Both enantiomers of *threo*-1,2-diphenyl-2-aminoethanol are also commercially available, albeit only in small quantities ($110/500 mg, Sigma Aldrich).

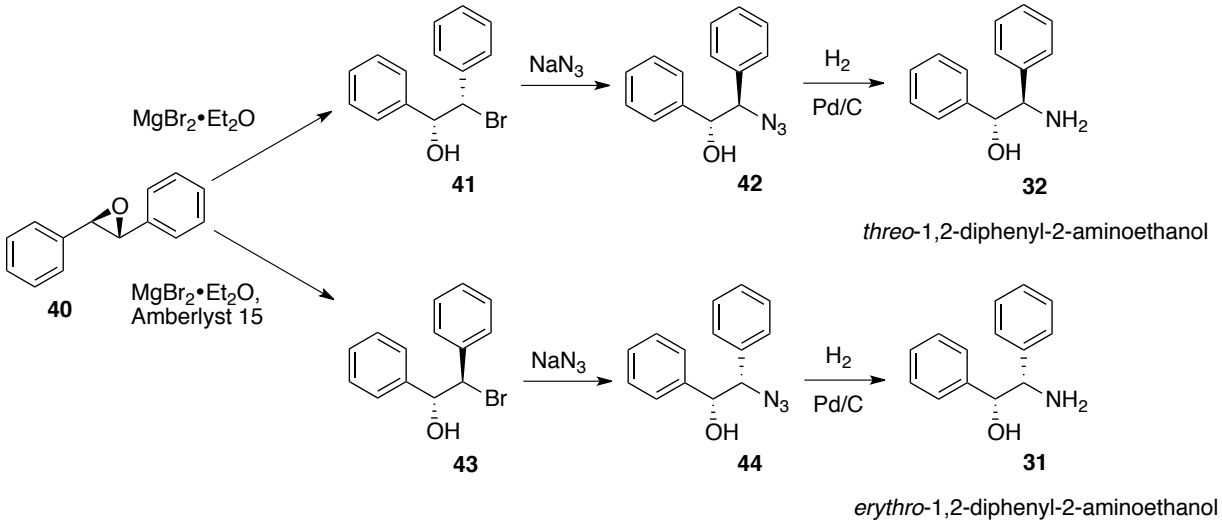


Scheme 2.3 Tishler's synthesis and resolution of *erythro*-1,2-diphenyl-2-aminoethanol and synthesis of *threo*-1,2-diphenyl-2-aminoethanol.

In 2003, Lupattelli and co-workers developed another method of synthesizing *erythro*-1,2-diphenyl-2-aminoethanol and *threo*-1,2-diphenyl-2-aminoethanol from *trans*-stilbene oxide.[14] The *trans* epoxide **40** is opened with magnesium bromide and Amberlyst 15 to give either the *cis*- or *trans*-bromohydrins **41/42**. The two diastereomers

[14] Lupattelli, P.; Bonini, C.; Caruso, L.; Gambacorta, A. *J. Org. Chem.* **2003**, *68*, 3360-3362.

can be transformed to the corresponding amino alcohols by direct displacement of the bromide with sodium azide followed by catalytic hydrogenation. The amino alcohols (**32**/**31**) were isolated in >95% yield and high ee (99% ee), Scheme 2.4. This reaction has only been performed on a small scale (~100 mg); the cost of *trans*-stilbene oxide may be an issue.



Scheme 2.4 Lupattelli's synthesis of *erythro*-1,2-diphenyl-2-aminoethanol and *threo*-1,2-diphenyl-2-aminoethanol from *trans*-stilbene oxide.

Erythro-1,2-diphenyl-2-aminoethanol (1*R*,2*S* or 1*S*,2*R*) has been used as a chiral auxiliary and ligand in asymmetric synthesis. In 1986, Robert Williams published the use (1*R*,2*S*)-1,2-diphenyl-2-aminoethanol to synthesize amino acids (Scheme 2.5).[15] The electrophilic glycinates **45** (lactones derived from the condensation of *erythro*-1,2-diphenyl-2-aminoethanol and glycine derivatives) were brominated with *N*-bromosuccinimide to yield bromoglycinate **46** in almost quantitative yield. Bromoglycinate **46** was found to be very reactive toward a variety of carbon nucleophiles. The resulting amino acids **48** were isolated in moderate yields with high enantioselectivities (>96% ee). This methodology complemented the existing enolate-based methodology of synthesizing amino acids. Then, in 1988, Williams developed an enolate-based alkylation protocol: deprotonation of **45** with lithium hexamethyldisilylazide at –80 ºC followed by alkyl halide addition; then, in 1991, he extended this methodology to form α,α-disubstituted amino acids **51**.[16]

In collaboration with Yutaka Aoyagi, Williams developed a new route to *erythro*-1,2-diphenyl-2-aminoethanol starting from the resolution of benzoin **52** with lipase TL® to yield (*S*)-acetate **53** (>99:1 er) and pure (*R*)-benzoin **52** (96:4 er), oxime formation with hydroxylamine hydrochloride followed by catalytic hydrogenation to yield enantiomerically pure *erythro*-1,2-diphenyl-2-aminoethanol (99:1 er), Scheme 2.6.[17] This

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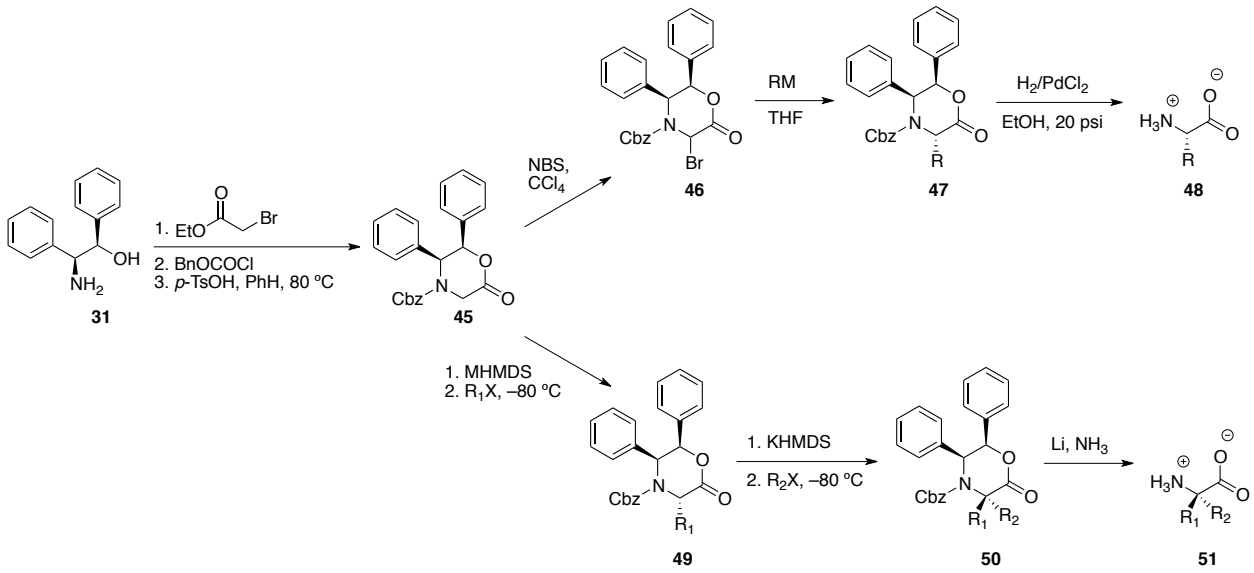
[15] (a) Sinclair, P. J.; Zhai, D.; Reibenspies, J.; Williams, R. M. *J. Am. Chem. Soc.* **1986**, *108*, 1103-1104. (b) Williams, R. M.; Sinclair, P. J., Zhai, D.; Chen, D. *J. Am. Chem. Soc.* **1988**, *110*, 1547-1557. (c) Williams, R. M.; Fegley, G. J. *J. Am. Chem. Soc.* **1991**, *113*, 8796-8806. (d) Williams, R. M; Zhai, W.; Aldous, D. J.; Aldous, S. C. *J. Org. Chem.* **1992**, *57*, 6527-6532.

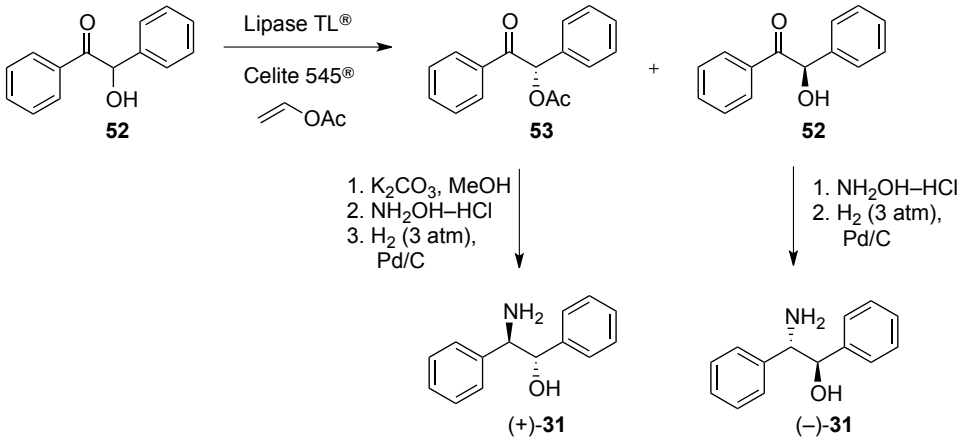
[16] (a) Williams, R. M.; Im, M. N. *Tetrahedron Lett.* **1988**, *29*, 6075-6078. (b) Williams, R. M.; Im, M. N. *J. Am. Chem. Soc.* **1991**, *113*, 92766-9286.

[17] Aoyagi, Y.; Iijima, A.; Williams, R. M. *J. Org. Chem.* **2001**, *66*, 8010-8014.

method has the disadvantage that a large amount of lipase (9.4 g) is required to resolve benzoin (3.7 g).

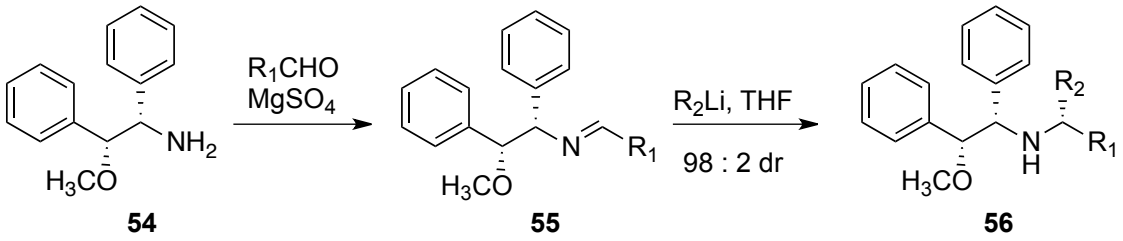


Scheme 2.5 Williams' synthesis of amino acids using *erythro*-1,2-diphenyl-2-aminoethanol as a chiral auxiliary.



Scheme 2.6 Williams' synthesis of *erythro*-1,2-diphenyl-2-aminoethanol from benzoin.

Another use of *erythro*-1,2-diphenyl-2-aminoethanol as a chiral auxiliary is in the synthesis of chiral amines from imines. In 1995, Hashimoto et al. reported the diastereoselective addition of various organolithium reagents to chiral imines **55**, synthesized by the condensation of aldehydes and *erythro*-2-methoxy-1,2-diphenylethylamine (Scheme 2.7).[18] The yields were moderate (43–89%) but the selectivities were high (~98:2 dr).

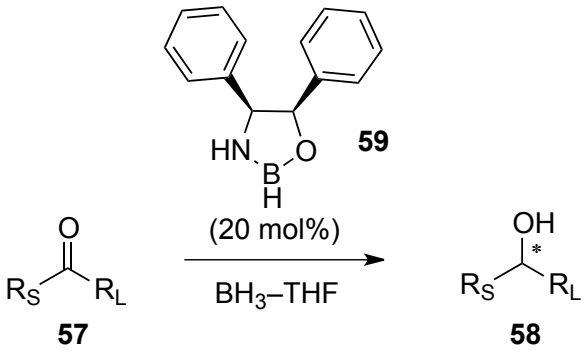


Scheme 2.7 Hashimoto's use of *erythro*-1,2-diphenyl-2-aminoethanol as a chiral auxiliary.

Erythro-1,2-diphenyl-2-aminoethanol has also been used as a chiral ligand in various processes. One example is the enantioselective reduction of ketones with (4*S*,5*R*)-4,5-diphenyl-1,3,2-oxazaborolidine **59**.[19] Aromatic alcohols were obtained in high yields (>90%) and moderate to high enantiomeric excess (66 – >99% ee); while aliphatic alcohols were obtained in moderate yields (~60%) and poor enantiomeric excess (~20% ee) (Scheme 2.8).

[18] Hashimoto, Y. Takaoki, K.; Sudo, A.; Ogasawara, T.; Saigo, K. *Chem. Lett.* **1995**, 235-236.

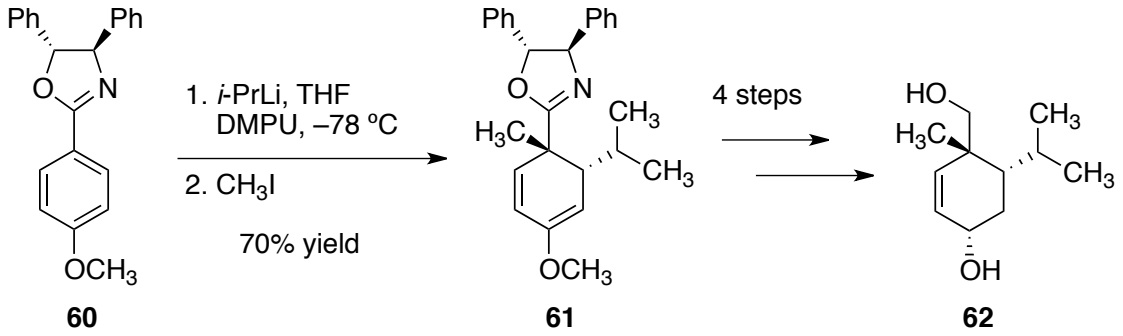
[19] Yaozhong, J.; Yong, Q.; Aiqiao, M.; Zhitang, H. *Tetrahedron: Asymm.* **1994**, *5*, 1211-1214.



Scheme 2.8 Use of *erythro*-1,2-diphenyl-2-aminoethanol as a chiral ligand in enantioselective reduction of ketones.

Threo-1,2-diphenyl-2-aminoethanol has also been used as a chiral auxiliary in synthesis. An example is the DMPU-promoted dearomatization of 4,5-diphenyloxazoline **60** (Scheme 2.9).[20] Product **61** is obtained from the nucleophilic attack of *iso*-propyllithium, which is presumably activated in the presence of DMPU to form ion pairs, followed by dearomatization and quenching with iodomethane, only one diastereomer is observed. After further elaboration of the substrate, the auxiliary can be removed by hydrolysis.

[20] Clayden, J.; Parris, S.; Cabedo, N.; Payne, A. H. *Angew. Chem. Int. Ed.* **2008**, *47*, 5060-5062.

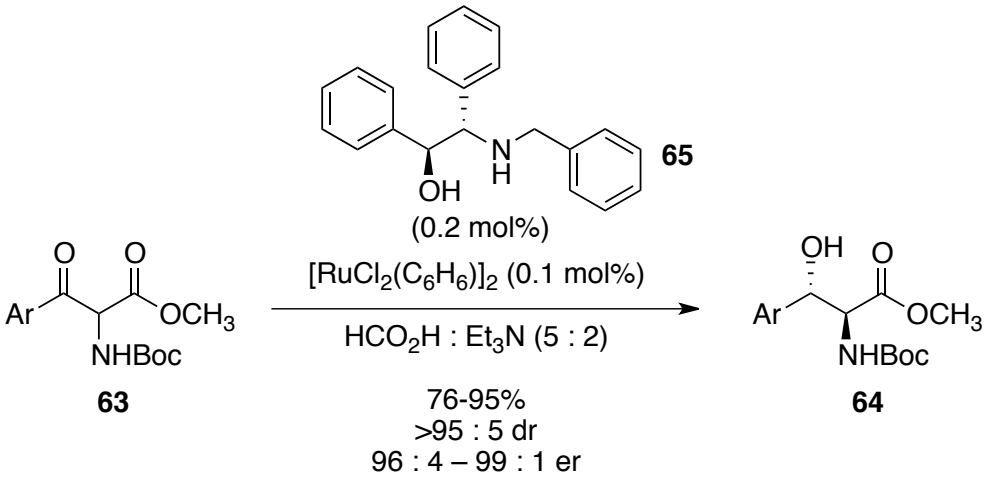


60 **61** **62**

Scheme 2.9 Use of *threo*-1,2-diphenyl-2-aminoethanol as a chiral auxiliary in the dearomatization of 4,5-diphenyloxazolines.

Threo-1,2-diphenyl-2-aminoethanol has also been used as a chiral ligand. An example is an *N*-benzyl-*threo*-1,2-diphenyl-2-aminoethanol (**65**)–ruthenium complex, which has been used to synthesize *anti*-β-hydroxy-α-amido esters by transfer hydrogenation.[21] The catalyst is added to a β-keto ester **63** in the presence of a formic acid:triethylamine (5:2) complex. The desired products **64** are isolated in good yields (76–95%), high dr's (>95:5 dr), and high er's (96:4 – 99:1 er), Scheme 2.10.

[21] Seashore-Ludlow, B.; Villo, P.; Hacker, C.; Somfai, P. *Org. Lett.* **2010**, *12*, 5274-5277.



Scheme 2.10 Use of a *threo*-1,2-diphenyl-2-aminoethanol derivative as a chiral ligand in the catalytic asymmetric transfer hydrogenation of β-keto esters.

Synthesis and Use of Ephenamine

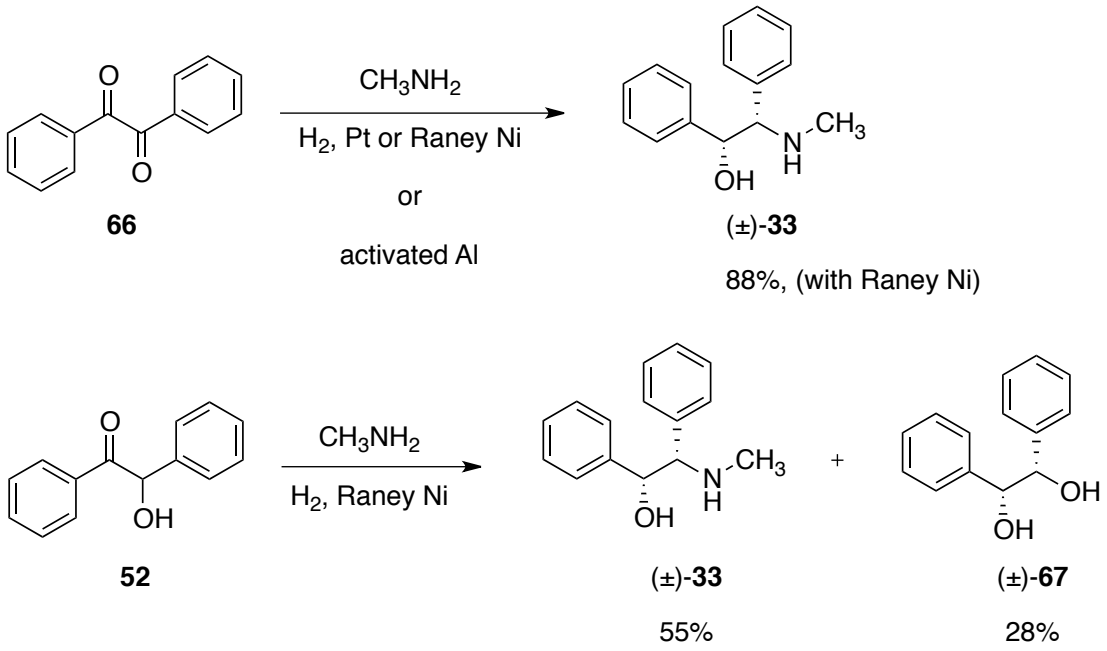
Racemic ephenamine **33**, (*R*,*S*)-2-methylamino-1,2-diphenylethanol, has been synthesized from the condensation of benzil **66** and methylamine followed by catalytic hydrogen in the presence of platinum[22] or Raney nickel[23] or with activated aluminum.[24] It has also been synthesized from the condensation of benzoin **52** and methylamine followed by catalytic hydrogenation with Raney nickel, albeit with a lower yield (55% vs. 88%); *meso*-hydrobenzoin **67** was isolated as a by-product (Schemes 2.11).[23]

[22] (a) Skita, A.; Keil, F. U. K. Patent 313,617, July 24, 1930. (b) Skita, A.; Keil, F. German Patent 603 670, October 5, 1934.

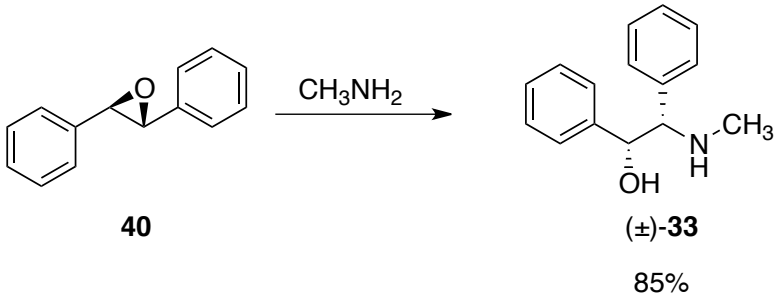
[23] Wheatley, W. B.; Fitzgibbon, W. E.; Cheney, L. C. *J. Org. Chem.* **1953**, *18*, 1564-1571.

[24] Knoll, A. G.; Klavehn, W. German Patent 535 839, May 29, 1931.

Ephenamine has also been synthesized by the opening of *trans*-stilbene oxide with methylamine (85% yield), Scheme 2.12.[25]



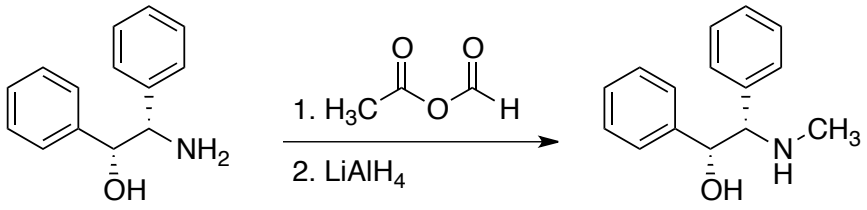
Scheme 2.11 Synthesis of racemic ephenamine from benzil or benzoin and methylamine.



Scheme 2.12 Synthesis of racemic ephenamine from *trans*-stilbene oxide and methylamine.

[25] Anderson, W. K.; Milowsky, A. S. *J. Med. Chem.* **1986**, *29*, 2241-2249.

Racemic ephenamine has been resolved with penicillin salts to obtain optically pure amino alcohol.[23] Optically pure ephenamine[26] has been prepared following the Tishler synthesis[13] of *erythro*-1,2-diphenyl-2-aminoethanol followed by *N*-formylation with acetic formic anhydride then by reduction with lithium aluminum hydride (Scheme 2.13).[27]



31 **33**

Scheme 2.13 Synthesis of optically pure ephenamine.

(+ or –)-Ephenamine-penicillin salts have been used as antibiotics and feed additives to promote growth in poultry and livestock.[28] Ephenamine-glutamine salts have also been prepared to provide effective amounts of glutamine for human consumption.[29] Ephenamine has also been used to resolve penicillin[30] and glycine derivatives.[31]

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[26] Gamsey, S.; DeLaTorre, K.; Singaram, B. *Tetrahedron: Asymm.* **2005**, *16*, 711-715.

[27] Effenberger, F.; Gutterer, B.; Jager, J. *Tetrahedron: Asymm.* **1997**, *8*, 459-467.

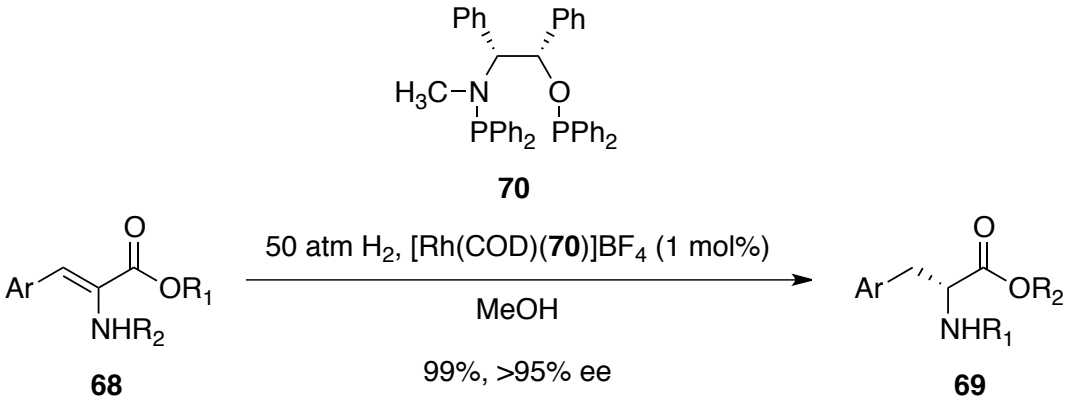
[28] (a) Young, V. V. (Commerical Solvents Corporation) U. K. Patent 682,931, November 19, 1952. (b) Gerard, W. E.; Read, D. C.; Pensack, J. M. *J. Agric. Food Chem.* **1953**, *1*, 784-788. (c) Buckwalter, F. H. U. S. Patent 2,768,081, October 23, 1956. (d) Federal Registrar May 17, 1969.

[29] (a) Baxter, J. H. U. S. Patent US 2003/0099722 A1, May 29, 2003. (b) Baxter, J. H. U. S. Patent US 2003/0134851 A1, July 17, 2003.

[30] Sheehan, J. C.; Henery-Logan, K. R. *J. Am. Chem. Soc.* **1959**, *81*, 3089-3094.

[31] Weber, A.; Bouzard, P.; Bouzard, D. U. S. Patent 3,803,213, April 9, 1974.

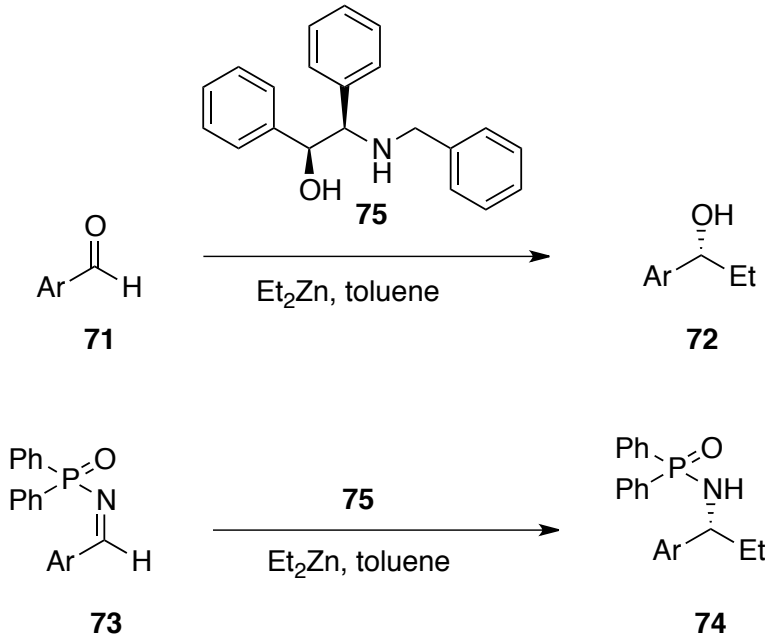
An aminophosphine phosphinite-derived ligand of ephenamine (**70**) has been used in the catalytic asymmetric hydrogenation of dehydroamino acids (Scheme 2.14).[32] The reaction proceeds with a catalytic amount of a rhodium-ligand complex and 50 atmospheres of hydrogen gas in methanol. The amino acids are obtained in quantitative yields and excellent ee's (>95% ee). *N*-Benzylephenamine **75**, among other ephenamine derivatives, has also been used as a chiral ligand for the asymmetric addition of diethylzinc to aldehydes and diphenylphosphinoylimines (Scheme 2.15).[33]



Scheme 2.14 The use of an ephenamine-derived chiral ligand in the catalytic asymmetric hydrogenation of dehydroamino acids.

[32] (a) Mi, A.; Lou, R.; Jiang, Y.; Deng, J.; Qin, Y.; Fu, F.; Li, Z.; Hu, W.; Chan, A. S. C. *Synlett* **1998**, 847-848. (b) Xie, Y.; Lou, R.; Li, Z.; Mi, A.; Jiang, Y. *Tetrahedron: Asymm.* **2000**, *11*, 1487-1494. (c) Lou, R.; Mi, A.; Jiang, Y.; Qin, Y.; Li, Z.; Fu, F.; Chan, A. S. C. *Tetrahedron* **2000**, *56*, 5857-5863.

[33] (a) Zhang, H.-L.; Jaing, F.; Zhang, X.-M.; Cui, X.; Gong, L.-Z.; Mi, A.; Jiang, Y.-Z.; Wu. Y. *Chem. Eur. J.* **2004**, *10*, 1481-1492. (b) Banerjee, S.; Camodeca, A. J.; Griffin, G. G.; Hamaker, C. G.; Hitchcock, S. R. *Tetrahedron: Asymm.* **2010**, *21*, 549-557.



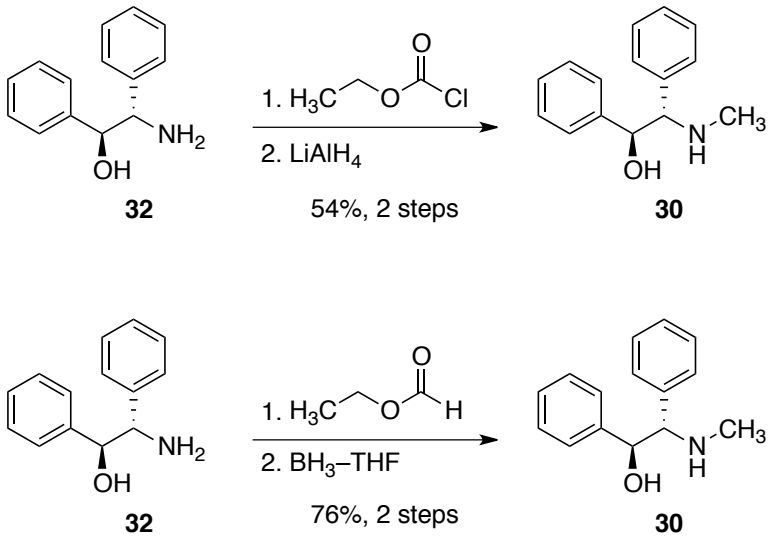
Scheme 2.15 The use of an ephenamine-derived chiral ligand in the catalytic asymmetric addition of diethylzinc to aldehydes and diphenylphosphinoylimines.

Synthesis and Use of Pseudoephenamine

Pseudoephenamine **30** has been synthesized following the Tishler protocol[13] for converting *erythro*-1,2-diphenyl-2-aminoethanol to *threo*-1,2-diphenyl-2-aminoethanol. *N*-Methylation was achieved by carbamate formation with ethylchloroformate followed by lithium aluminum hydride[34] or by formamide formation with ethyl formate followed by borane-tetrahydrofuran reduction (Scheme 2.16).[35]

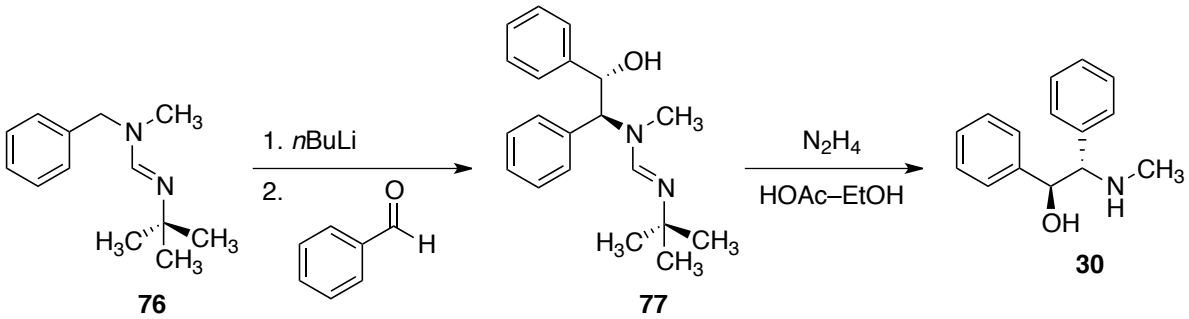
[34] Yamashita, J.; Kawahara, H.; Ohashi, S.; Honda, Y.; Kenmotsu, T.; Hashimoto, H. *Tech. Rep. Tohoku University* **1983**, *48*, 211-219.

[35] Lou, R.; Mi, A.; Jiang, Y.; Qin, Y.; Li, Z.; Fu, F.; Chan, A. S. C. *Tetrahedron* **2000**, *56*, 5857-5863.



Scheme 2.16 Synthesis of (–)-pseudoephenamine.

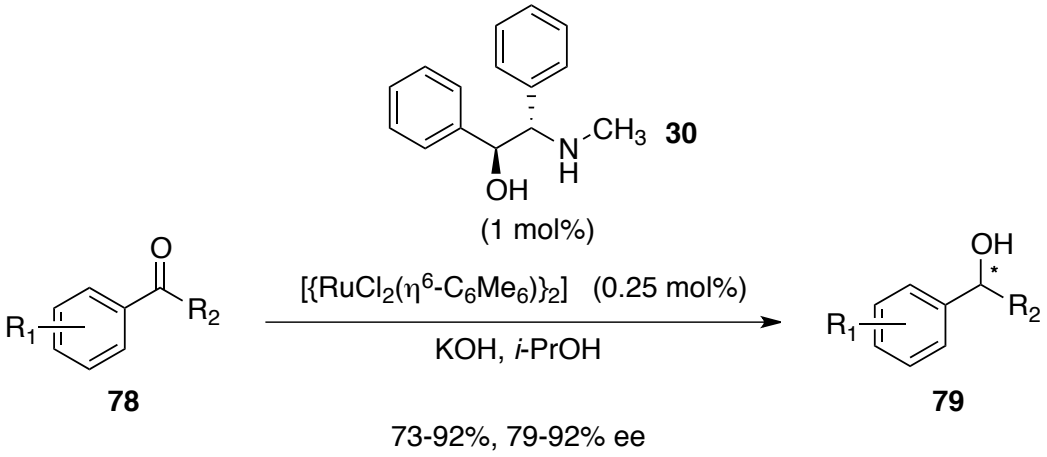
Meyers and co-workers also reported a synthesis of pseudoephenamine.[36] Formamidine **76** is deprotonated with *n*-buytllithium and alkylated with benzaldehyde to yield **77**; hydrazinolysis yields a single amino alcohol (pseudoephenamine), which was assigned the *syn* configuration based on proton coupling constants (Scheme 2.17).



Scheme 2.17 Meyers' synthesis of pseudoephenamine.

[36] Meyers, A. I.; Marra, J. M. *Tetrahedron Lett.* **1985**, *26*, 5863-5866.

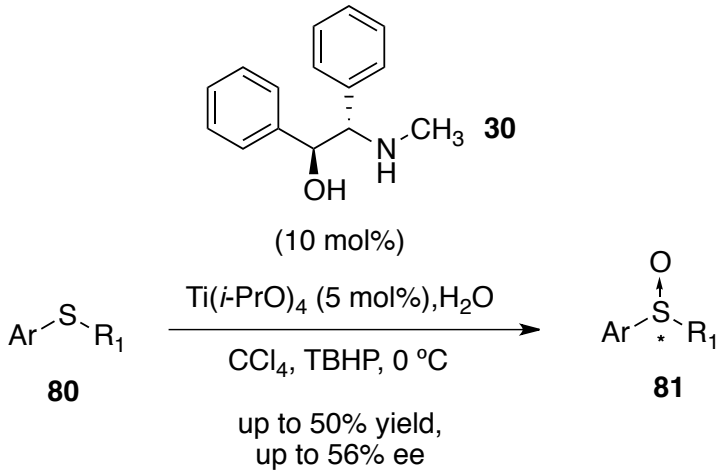
Pseudoephenamine has limited reported use as a chiral ligand or auxiliary. An example as a chiral ligand is the catalytic asymmetric transfer hydrogenation of ketones.[37] The reduction occurs with a catalytic amount of a ruthenium (II)–amino alcohol complex in isopropanol. The alcohols are isolated in good yields (73–92%) and good ee's (79–97% ee), Scheme 2.18. Another example as a chiral ligand is the catalytic asymmetric oxidation of sulfides.[38] The oxidation occurs with a catalytic amount of a titanium (IV)–amino alcohol complex, with *tert*-butyl hydroperoxide as the oxidant. The sulfoxides are isolated in ~50% yield and ~50% ee (Scheme 2.19).



Scheme 2.18 The use of (–)-pseudoephenamine as a chiral ligand in the catalytic asymmetric transfer hydrogenation of aromatic ketones.

[37] Takehara, J.; Hashiguchi, S.; Fujii, A.; Inoue, S.; Ikariya, T.; Noyori, R. *Chem. Commun.* **1996**, 233-234.

[38] Peng, Y.; Feng, X.; Cui, X.; Jiang, Y.; Choi, M. C. K.; Chan, A. S. C. *Synth. Commun.* **2003**, *33*, 2793-2801.

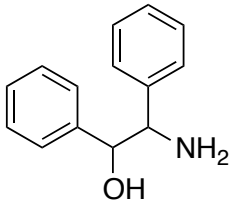


Scheme 2.19 The use of (–)-pseudoephenamine as a chiral ligand in the catalytic asymmetric oxidation of sulfides.

Biological Activity of Related Compounds

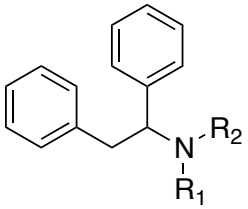
The following compounds exhibited a small amount of analgesic activity and antiepileptic activity in mice and rats: 2-amino-1,2-diphenyethanol **31/32** and 1,2-diphenylethylamines (methamphetamine derivative) **82** (Figure 2.2).[39] These compounds were significantly less effective than the drugs on the market in relieving the symptoms in rodents. Pseudoephenamine was found to have no reported biological activity.

[39] (a) Dodds, E. C.; Lawson, W.; Williams, P. C. *Nature* **1943**, *151*, 614-615. (b) Holck, H. G. O.; Kimura, K. K.; Kimura, T. E. *J. Am. Pharm. Assoc.* **1950**, *39*, 354-359. (c) Griffith, R. C. European Patent 0 287 089 A2, August 17, 1988. (b) Griffith, R. C.; Napler, J. J. European Patent 0 279 937 A1, August 31, 1988. (d) Griffith, R. C. European Patent 0 326 240 A1, August 2, 1989.



31/32

2-amino-1,2-diphenylethanol



82

1,2-diphenylethylamine

Figure 2.2 Structure of related compounds with biological activity

Chapter 3

Pseudoephenamine: A Practical Chiral Auxiliary for Asymmetric Synthesis

Introduction

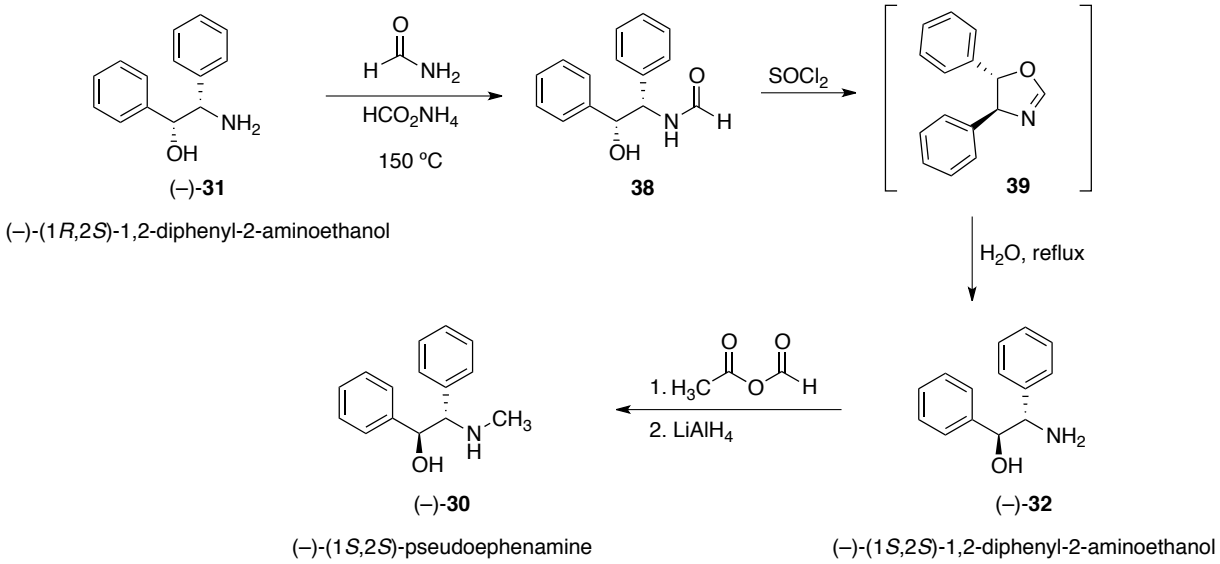
Pseudoephedrine has been used as a chiral auxiliary in diastereoselective alkylation reactions, providing easy access to enantiomerically enriched carboxylic acids, alcohols, ketones, and aldehydes.[1] Because pseudoephedrine can be transformed into methamphetamine and other illegal drugs, many countries restrict or ban its sale and distribution, which complicate its use in academic and industrial settings. In this chapter, we show that (1*S*,2*S*)-2-methylamino-1,2-diphenylethanol and (1*R*,2*R*)-2-methylamino-1,2-diphenylethanol (synonymously, (1*S*,2*S*)- and (1*R*,2*R*)-pseudoephenamine, respectively) enable a broad range of utilities in asymmetric synthesis that meet or exceed those that previously characterized the pseudoephedrine system alone, with several advantages.[9] First, these auxiliaries are free from regulatory restrictions and are not known to be transformable into illegal substances; second, asymmetric alkylation reactions that employ pseudoephenamine as a chiral auxiliary proceed with equal or greater diastereoselectivities than the corresponding reactions employing pseudoephedrine, with notable improvements in the selectivities of the alkylation reactions that form quaternary carbon stereocenters; and lastly, amides derived from pseudoephenamine exhibit a greater propensity to be crystalline compounds than the corresponding pseudoephedrine derivatives.

Synthesis of (1*S*,2*S*)- and (1*R*,2*R*)-Pseudoephenamine

Both enantiomers of pseudoephenamine are easily prepared using well-established methods, Scheme 3.1. We have applied the Tishler protocol,[13] with a small

but important modification, for the large-scale synthesis of both enantiomers of *threo*-1,2-diphenyl-2-aminoethanol from the appropriate *erythro*-diastereomer. The Tishler method involves converting *erythro*-1,2-diphenyl-2-aminoethanol (1*R*,2*S* or 1*S*,2*R*) to *threo*-1,2-diphenyl-2-aminoethanol (1*S*,2*S* or 1*R*,2*R*) by *N*-formylation with formamide, invertive cyclization to form the corresponding oxazoline **39** using thionyl chloride, and hydrolytic ring-opening under acidic conditions. We found we were able to obtain the desired formylated product **38** in high yield (>98%) using formamide containing 0.2 equivalent of ammonium formate for *N*-formylation rather than pure formamide, which leads to yellowing and a reduced yield (~70%) of the product. The crude *threo*-1,2-diphenyl-2-aminoethanol is recrystallized from hot ethanol to obtained needle-like crystals, 92% yield; melting point and optical rotation matched to those previously reported. Subsequent *N*-methylation of *threo*-1,2-diphenyl-2-aminoethanol is achieved in 97% yield by *N*-formylation with acetic formic anhydride followed by reduction with lithium aluminum hydride.[27] The crude product, **30**, is pure by ^{1}H NMR analysis and can be used directly for amide synthesis. We have routinely prepared 20–40-g batches of (1*S*,2*S*)- and (1*R*,2*R*)-pseudoephenamine by this four-step method in 87% overall yield, which requires no column chromatography. Pseudoephenamine can be recrystallized from hot ethanol to produce large, orthorhombic, colorless crystals (mp = 109–110 ºC).[40] X-ray crystallographic analysis revealed that pseudoephenamine adopts a conformation identical to pseudoephedrine in the solid state; with gauche interactions between both the aminomethyl and hydroxyl groups as well as the two phenyl substituents, Figure 3.1.

[40] A prior synthesis of (1*S*,2*S*)-pseudoephenamine described the compound as a white, needle-like solid (mp 125–126 ºC). Lou, R.; Mi, A.; Jiang, Y.; Qin, Y.; Li, Z.; Fu, F.; Chan, A. S. C. *Tetrahedron* **2000**, *56*, 5857-5863.



Scheme 3.1 Synthesis of (–)-(1*S*,2*S*)-pseudoephenamine by a modified Tishler protocol.

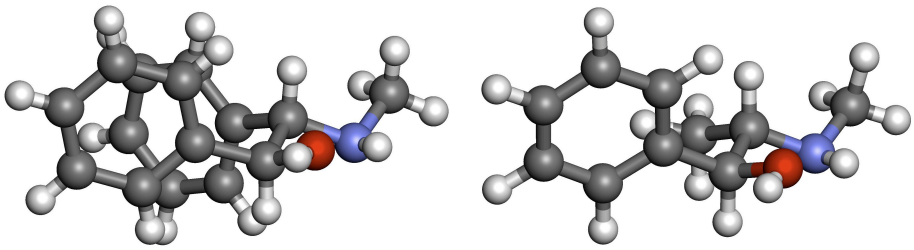


Figure 3.1 X-ray crystal strucures of (–)-pseudoephenamine and (+)-pseudoephedrine.[41]

[41] (a) The pseudoephedrine crystal structure was obtained from the Cambridge Crystallographic Database (PSEPED01). Mathew, M.; Palenik, G. J. *Acta. Cryst.* **1977**, *B33*, 1016-1022. (b) The hydrogen atoms of the benzene ring of pseudoephedrine were regenerated at idealized positions using DS Visualizer. Allen, F. H. *Acta. Cryst.* **2002**, *B58*, 380-388.

Synthesis of Pseudoephenamine Amides

Pseudoephenamine amides were prepared from the corresponding carboxylic acid chlorides or anhydrides by routine methods (see Experimental Section). Of the amides prepared, most were crystalline solids except for α-pentylacrylamide **88** and α-ethylacrylamide **89**, which were syrup-like. Figure 3.2 depicts the pseudoephenamine amides that were prepared in this study along with their melting points, if applicable; for comparison, the melting points of the pseudoephedrine amide derivatives are given in parenthesis. For those amides that were solids, the pseudoephenamine amide melting points were significantly higher than the pseudoephedrine amides. X-ray crystallographic analysis of (1*S*,2*S*)-pseudoephenamine propionamide **83** showed that the molecule adopts a conformation with the amido and hydroxyl groups in a gauche relationship, as well as the two phenyl substituents (see Experimental Section).

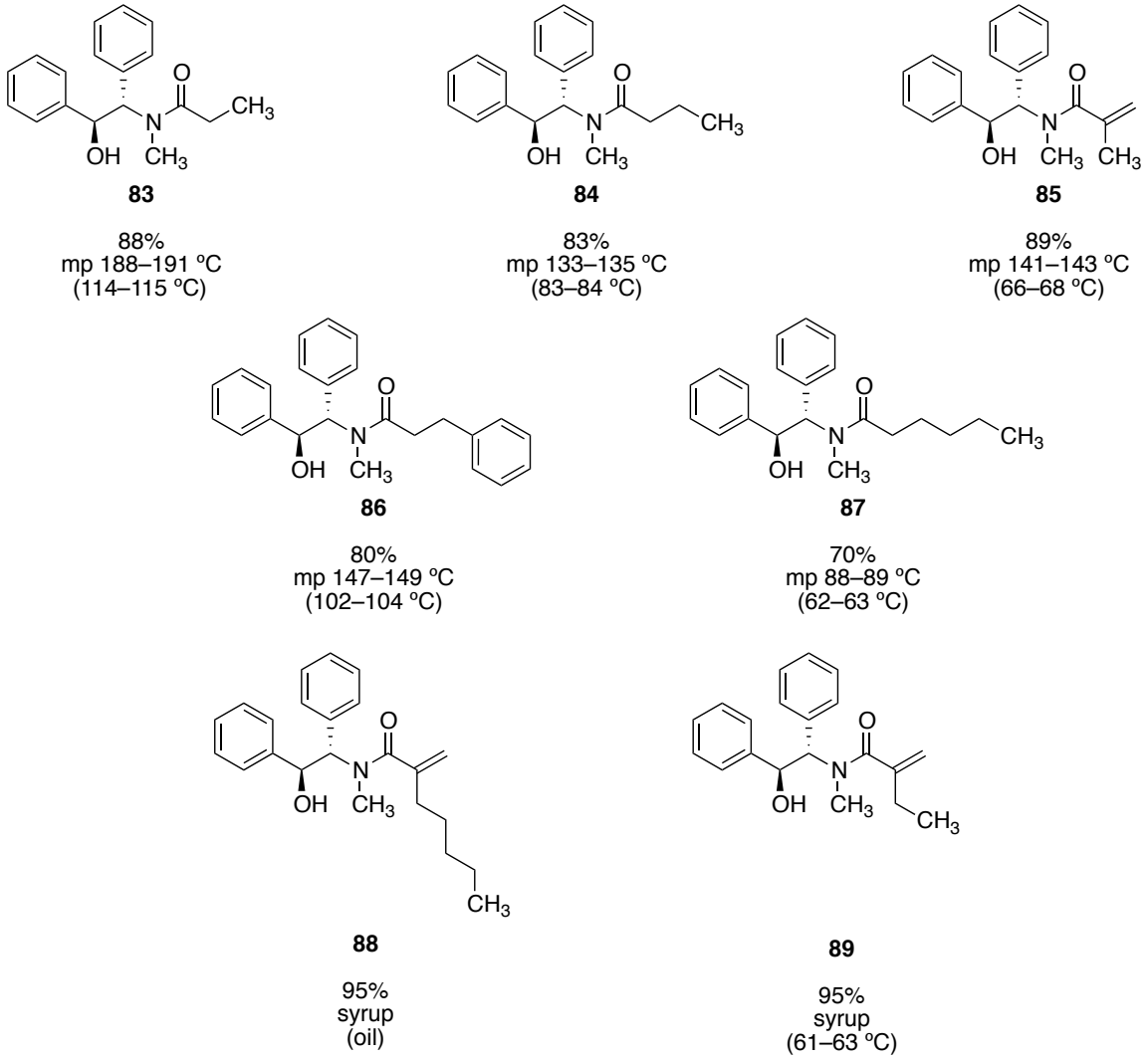


Figure 3.2 Pseudoephenamine amides prepared as substrates in this work.

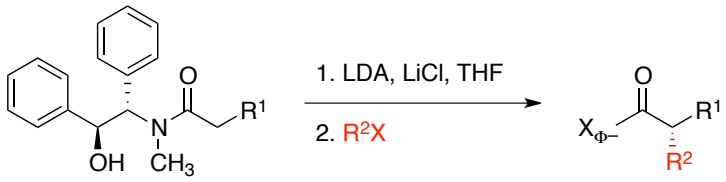
Diastereoselective Alkylation of Pseudoephenamine Amides

Pseudoephenamine amide enolates were generated with conditions identical to those used for enolization of pseudoephedrine amides; pseudoephenamine amides were treated with lithium diisopropylamide (2.2 equiv) in tetrahydrofuran (THF) at –78 ºC in the presence of anhydrous lithium chloride (6 equiv). Pseudoephenamine propionamide

was not soluble in THF alone, a 1:1 mixture of THF-pyridine proved to be a viable reaction solvent in this case (also in the presence lithium chloride). The procedure involves transferring a solution of amide in THF to the lithium diisopropylamide-lithium chloride mixture at –78 ºC. The suspension is held at –78 ºC for 1 h, and then is warmed to 0 ºC for 15 min, and briefly at 23 ºC, then is cooled to 0 or –78 ºC and treated with an alkylating agent (≥1.5 equiv).[42] (Table 3.1) The products were isolated in 84–99% yields (after purification by recrystallization or column chromatography) and with uniformly high diastereoselectivities (isolated dr ranged from 98:2 to ≥99:1). Reaction diastereoselectivities were measured by HPLC analysis of the products with the exception of entries 1 and 7, Table 3.1, where the trimethylsilyl ethers were used. We also found that the diastereoselectivities could also be assessed by ^{1}H NMR analysis of the corresponding oxazolinium triflate derivatives, obtained by invertive cyclization with triflic anhydride.[6] Diastereoselectivities were uniformly high, as in the corresponding alkylation reactions of pseudoephedrine amides. The absolute stereochemistry of the alkylation products was confirmed by X-ray crystallographic analysis of amide **90**, entry 1, Table 3.1 (see Experimental Section). We believe that the model proposed for the conformation of pseudoephedrine amide enolates[1b] applies to our case as well (Figure 3.3), where the phenyl group that replaced the methyl group occupies the same space, with some possible π-stacking interaction with the backbone phenyl group, because we observe a 1,4 *cis* relationship between the new phenyl group and the new stereocenter. The majority of the alkylation products were solids.

[42] Because pseudoephenamine propionamide was not soluble in THF, a different addition method was tried; lithium diisopropylamide in THF was transferred to a suspension of propionamide and lithium chloride in THF. After warming to 0 ºC, the majority of the solids dissolved (presumably all the propionamide was in solution as the enolate). When alkylating with benzyl bromide (entry 1, Table 3.1) the yield was lower (72 %) but the diastereoselectivity was the same (>99:1 dr).

Table 3.1 Diastereoselective alkylation of pseudoephenamine amides.



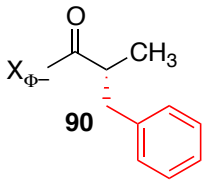
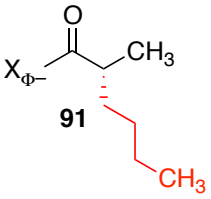
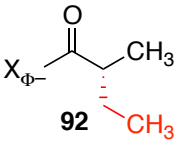
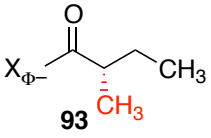
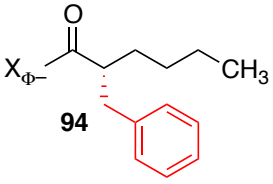
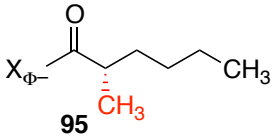
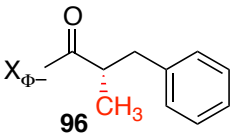
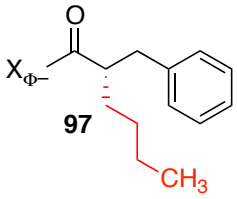
Entry[a]	Product	Crude dr[b]	Isolated dr[b]	Yield (%)	mp (°C)
1	 **90**	95:5	≥99:1	85	128–129
2	 **91**	95:5	98:2	97	NA
3	 **92**	≥94:6	98:2	96	NA
4	 **93**	≥96:4	≥99:1	87	89–90
5	 **94**	≥98:2	≥99:1	99	112–114
6	 **95**	95:5	98:2	84	77–79
7	 **96**	98:2	98:2	92	NA

Table 3.1 *continued*

8		≥99:1	≥99:1	99	109–111

[a] Entries 1, 2, and 3 were conducted in 1:1 THF-pyridine as solvent; all other entries were conducted in THF alone as solvent. All reactions were conducted with excess alkyl halide (1.5–4.0 equiv). [b] Diastereomeric ratios were determined by HPLC analysis; for entries 1 and 7, the corresponding trimethylsilyl ethers were analyzed by HPLC. NA=not applicable.

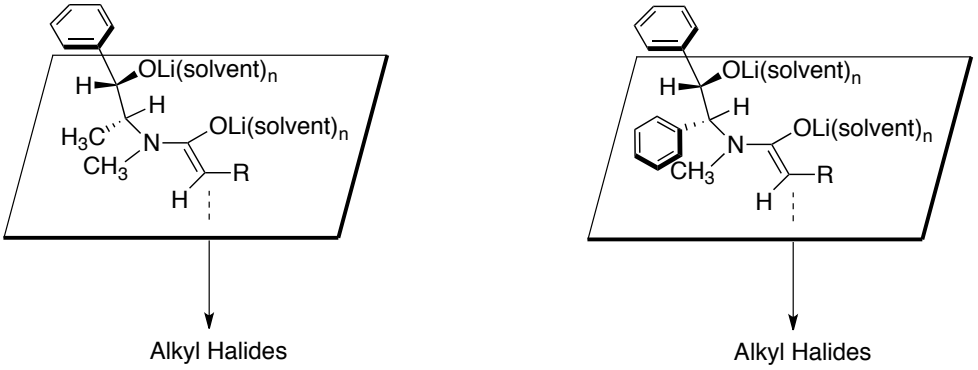
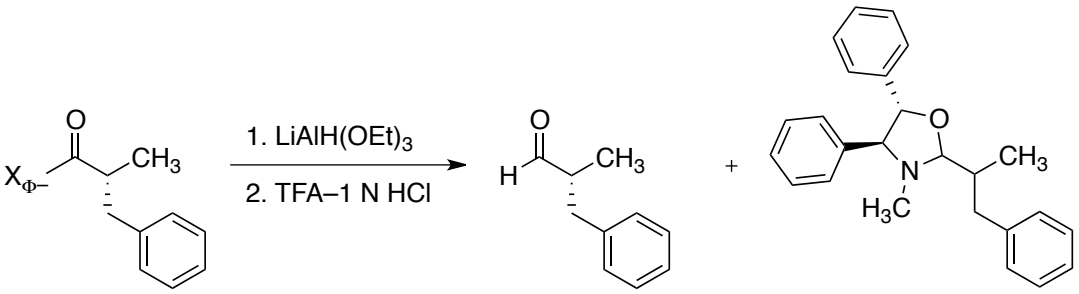


Figure 3.3 Proposed reactive conformations of pseudoephedrine and pseudoephenamine amide enolates.

Transformations of Pseudoephenamine Amides into Enantiomerically Enriched Carboxylic Acids, Ketones, and Alcohols

Optically active carboxylic acids, ketones, and alcohols were obtained directly from alkylated pseudoephenamine amides by using methods parallel to those previously employed for similar transformations of pseudoephedrine amides,[1a,b] Chart 3.1. Hydrolysis of pseudoephenamine amides under both acidic (9 N sulfuric acid in dioxane)

and basic (tertra-*n*-butylammonium hydroxide in a 3:1 *tert*-butyl alcohol in water) conditions provides carboxylic acids in high yield and high ee's (89–99%, 90–98 % ee) with little or no epimerization of the α-carbon center. Addition of organolithium reagents (*n*-buytllithium, phenyllithium, and methyllithium) affords enantiomerically enriched ketones in high yields and high ee's (95–98%, ≥93% ee).[43] Reduction of pseudoephenamine amides with lithium amidotrihydroborate (LAB)[5] gave the corresponding primary alcohols in high yields and high ee's (89–94%, 97–98% ee). Preliminary experiments exploring the direct transformation of pseudoephenamine amides to aldehydes using lithium triethoxyaluminum hydride as reductant have not yet provided high yields of product (30–60%, 70% ee). The problem we encounter is that not all intermediate **98** is hydrolyzed using trifluoroacetic acid-1 N hydrochloric acid, even upon heating or stirring for several hours (Scheme 3.2). Hemiaminal **98** is isolated after column chromatography.



90 **22** **98**

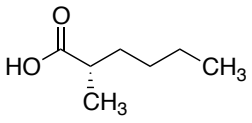
60%, 70% ee

Scheme 3.2 Reduction of pseudoephenamine amides with lithium triethoxyaluminum hydride.

[43] There was a slight modification to the procedure: trichloroacetic acid (≥93% ee, 96% yield) was used instead of acetic acid (89% ee and 90% yield) to decompose the tetrahedral intermediate of ketone **19**.

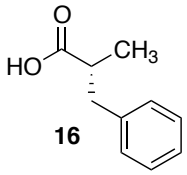
Chart 3.1 Transformations of pseudoephenamine amides into enantiomerically enriched carboxylic acids, alcohols, and ketones.

Carboxylic Acids (via acidic or basic hydrolysis):



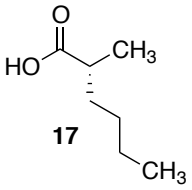
99

93%, 95% ee
97%, ≥95% ee



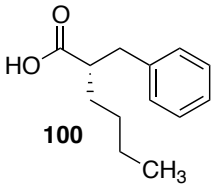
16

98%, 98% ee
99%, 95% ee



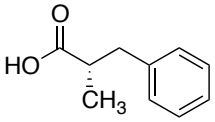
17

89%, 92% ee
94%, 91% ee



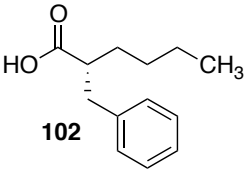
100

93%, ≥97% ee



101

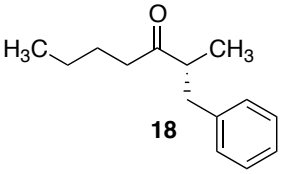
99%, 92% ee



102

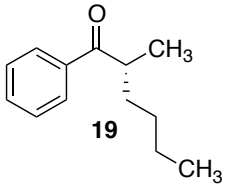
98%, 90% ee

Ketones (via aryl or alkyllithium addition):



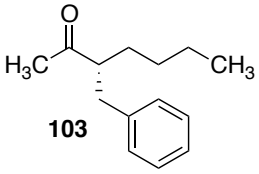
18

95%, ≥95% ee



19

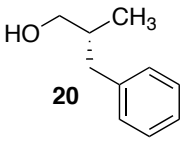
96%, ≥93% ee



103

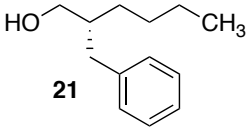
98%, ≥95% ee

Alcohols (via LAB reduction):



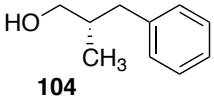
20

91%, 98% ee



21

89%, 95% ee



104

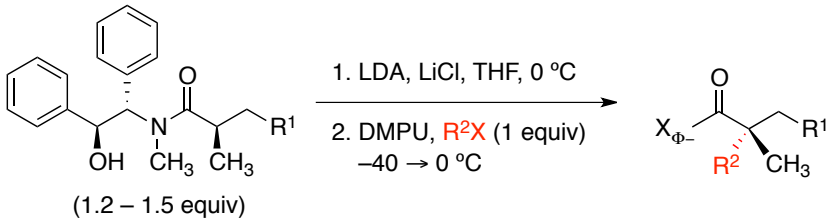
94%, 87% ee

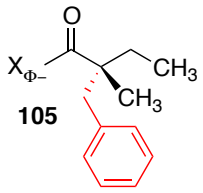
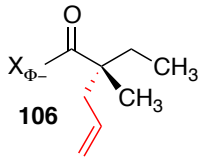
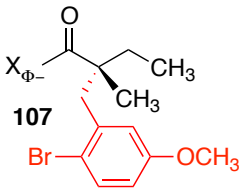
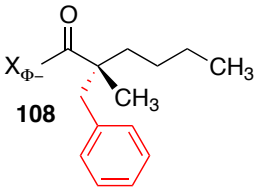
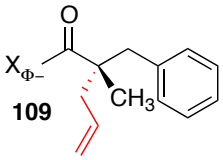
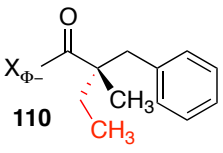
Stereocontrolled Construction of Quaternary Carbon Centers

Two methods for the alkylative construction of quaternary carbon centers using pseudoephenamine as a chiral auxiliary were investigated, and, in both cases, significant enhancements in diastereoselectivities were observed compared to the corresponding transformation with pseudoephedrine. The first method involved sequential enolization-alkylation of α,α-disubstituted pseudoephenamine amides, Table 3.2. The enolates were generated with conditions identical to those used for enolization of α,α-disubstituted pseudoephedrine amides (excess enolate, limiting electrophile).[44] The only difference was that the concentration of the reaction mixture was increased from 0.2 M to 0.3 M; yields were ~5-10% lower at the lower concentration. The isolated products were formed with ≥19:1 dr by ^{1}H NMR analysis of the corresponding oxazolinium triflate derivative (formed with triflic anhydride).[6] The only exception was compound **110** (entry 6, Table 3.2), which was isolated with a 9.9:1 dr. This case was due to the fact that an unactivated electrophile (iodoethane) was use, and that the reaction was conducted at 0 ºC for 24 h; the reaction seemed to stall at lower temperatures (yields ~50-60%). The diastereomers were separated by radial chromatography, facilitated by the UV activity of the auxiliary; the quaternary carbon center product diastereomers using pseudoephedrine were not separable by chromatography. The ^{1}H NMR spectra of the purified products were simplified by the fact that the products appeared to exist in a single rotameric form. X-ray crystallographic analysis of amide **105** (entry 1, Table 3.2) revealed that, in the solid state, this substance adopts the rotameric form in which the *N*-methyl group is *cis* to the quaternary center, and we believe that this is likely the case in solution as well.

[44] Reactions conducted with limiting enolate and excess electrophile were also low yielding, ~5-10% less.

Table 3.2 Quaternary carbon centers formed by enolization–alkylation of α,α-disubstituted pseudoephenamine amides.



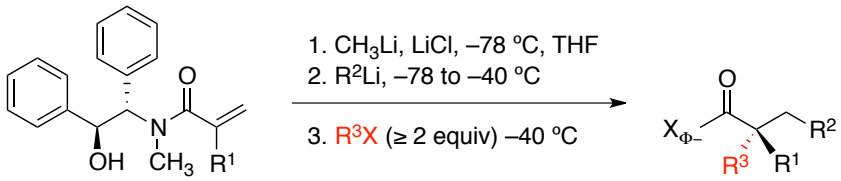
Entry	Product	Yield (%)	dr[a]
1	 **105**	83	≥19:1 (≥19:1)
2	 **106**	99	≥19:1 (14:1)
3	 **107**	91	≥19:1 (7.3:1)
4	 **108**	87	≥19:1 (8.3:1)
5	 **109**	82	≥19:1 (≥19:1)
6	 **110**	80	9.9:1[b] (6.2:1)

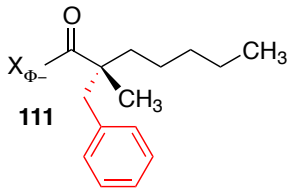
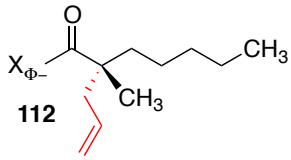
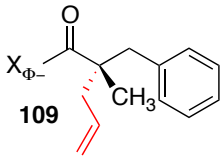
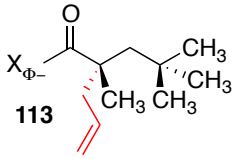
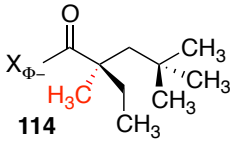
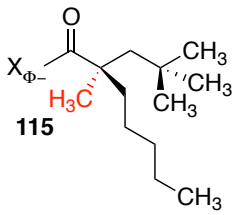
[a] Diastereomeric ratios in parentheses correspond to the analogous transformations with pseudoephedrine. [b] The product diastereomers were separated using radial chromatography.

The major diastereomer was isolated in 71% (≥19:1 dr), and the minor diastereomer was isolated in 6% yield (≥19:1 dr).

The second method involved conjugation addition-alkylation of α-alkyl-α,β-unsaturated pseudoephenamine amides,[3] Table 3.3. Kevin Mellem, a fellow graduate student, explored this method. The reaction conditions were identical to those used for α-alkyl-α,β-unsaturated pseudoephedrine amides. He found that in all the alkylation reactions, the ^{1}H NMR spectra of the crude reaction products were exceptionally clean, and, in many cases, the unpurified products appeared to be diastereomerically pure. As with the case above, the ^{1}H NMR spectra of the purified products were simplified by the fact that the products appeared to exist in a single rotameric form. The isolated products were formed with ≥19:1 dr by ^{1}H NMR analysis of the corresponding oxazolinium triflate derivative (formed with triflic anhydride).[6]

Table 3.3 Quaternary carbon centers formed by conjugate addition–alkylation of α-alkyl-α,β-unsaturated pseudoephenamine amides.



Entry	Product	Yield (%)	dr[a]
1	 **111**	75	≥19:1 (10.1:1)
2	 **112**	77	≥19:1 (11.1:1)
3	 **109**	80	≥19:1 (≥19:1)
4	 **113**	85	≥19:1 (12.5:1)
5	 **114**	79	≥19:1 (9.1:1)
6	 **115**	76	≥19:1 (8.2:1)

[a] Diastereomeric ratios in parentheses correspond to the analogous transformations with pseudoephedrine.

We also use the previously proposed model for the alkylation of α,α-disubstituted pseudoephedrine amides, in which the less bulky group is *cis* to the *N*-methyl group,[2] but this model does not explain the enhanced diastereoselectivities observed for the majority of the examples in Tables 3.2 and 3.3. The problem with this model arises from the observations that compounds **114** and **115** (entries 5 and 6, Table 3.3, respectively) are isolated in ≥19:1 dr; in both these cases, there are methylene hydrogens that should form unfavorable steric interactions in the enolate model, Figure 3.4. In these cases, the presumed *E*-enolate is just as selective (≥19:1 dr) as the *Z*-enolate and their reaction times (2–6 h at –40 ºC) are very similar. In the case of pseudoephedrine amides, there was a marked difference in reactivity (~2 h at 0 ºC or ~2–6 h at –40 ºC) and selectivity (~8:1 to ≥19:1 dr) between the *E*- and *Z*-enolates that led to the proposed reasoning to explain the differences observed between the two enolates. There must be other effects that can help rationalize the observed selectivities for example: a rigid conformation of the backbone of the auxiliary or some enhanced electronic effects from the nitrogen atom. Given the high propensity of crystallinity of the amides, we have attempted to obtain a crystal structure of a pseudoephenamine amide enolate to explain the high diastereoselectivites we observe, but with no success. As with the α,α-disubstituted amide products, the majority of the α-quaternary amide products are solids, whereas pseudoephedrine α-quaternary amide products are typically oils.

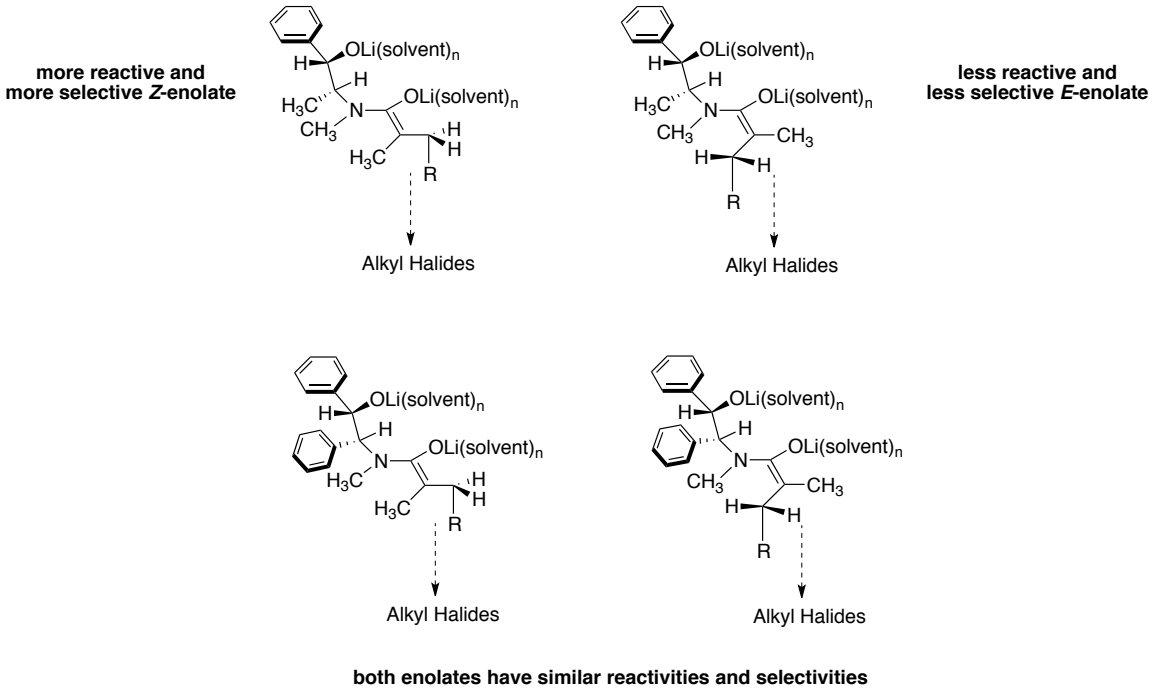


Figure 3.4 Proposed conformations of α,α-disubstituted pseudoephedrine and pseudoephenamine amide enolates.

Conclusions

Our findings suggest that, in many ways, pseudoephenamine is a superior chiral auxiliary for asymmetric synthesis when compared to pseudoephedrine. Advantages include the following: pseudoephenamine is free from regulatory restrictions; pseudoephenamine amides have physical properties that facilitate their physical processing and spectroscopic analysis (greater crystallinity and lack of line broadening in NMR spectra); and alkylation reactions that form amides with α-quaternary carbon

centers proceed with notably higher diastereoselectivities.[45] Although pseudoephenamine is not commercially available, it is easily prepared in large amounts from inexpensive starting materials.

[45] For a compelling illustration of the superior utility of pseudoephenamine versus pseudoephedrine in the alkylative construction of quaternary centers within a complex series of alkaloids, see: Medley, J. W.; Movassaghi, M. *Angew. Chem. Int. Ed.* **2012**, *51*, 4572–4576.

Experimental Section

General experimental procedures: All reactions were performed in flame-dried glassware fitted with rubber septa under a positive pressure of argon, unless otherwise noted. Air- and moisture-sensitive liquids were transferred via syringe or stainless steel cannula. Organic solutions were concentrated by rotary evaporation below 35 °C at 40 mmHg. Analytical thin-layer chromatography (TLC) was performed using glass plates pre-coated with silica gel (0.25-mm, 60-Å pore size, 230−400 mesh, Merck KGA) impregnated with a fluorescent indicator (254 nm). TLC plates were visualized by exposure to ultraviolet light (UV), then were stained by submersion in aqueous potassium permanganate solution (KMnO4), followed by brief heating on a hot plate (215 °C, 10−15 s). Flash column chromatography was performed as described by Still et al.,[46] employing silica gel (60 Å, standard grade) purchased from Dynamic Adsorbents.

Materials: Commercial solvents and reagents were used as received with the following exceptions. *N,N*- diisopropylamine was distilled from calcium hydride under an atmosphere of dinitrogen at 760 mmHg. 1,3-dimethyl-3,4,5,6-tetrahydro-2(1H)-pyrimidinone (DMPU) was distilled from calcium hydride under reduced pressure (0.1 mmHg) and stored under argon. Dichloromethane, ethyl ether, and tetrahydrofuran were purified by the method of Pangborn et al.[47] Lithium chloride was dried at 150 °C under vacuum (0.1 mmHg) for 12 h and stored in a drying oven at 150 °C (760 mmHg); the hot dried solid was flame dried under vacuum (0.1 mmHg) for 2−3 min immediately prior to use. Benzyl bromide, allyl bromide, iodobutane, iodoethane, and iodomethane were

[46] Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923–2925.

[47] Pangborn, A. B.; Giardello, M. A.; Grubbs, R. H.; Rosen, R. K.; Timmers, F. J. *Organometallics*. **1996**, *15*, 1518–1520.

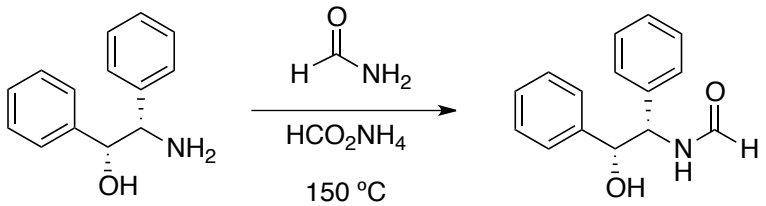
filtered through a column of oven-dried basic alumina, neat, immediately prior to use. The molarity of solutions of *n-butyllithium, t-butyllithium,* methyllithium, and phenyllithium was determined by titration against diphenylacetic acid as an indicator (average of three determinations).[48]

Instrumentation: Proton nuclear magnetic resonance spectra (^{1}H NMR) spectra and carbon nuclear magnetic resonance (^{13}C NMR) spectra were recorded on Varian INOVA 500 (500 MHz/125 MHz) or Varian INOVA 600 (600 MHz/150 MHz) NMR spectrometers at 23 °C. Proton chemical shifts are expressed in parts per million (ppm, δ scale) and are referenced to residual protium in the NMR solvent ($CHC1_3$: δ 7.26). Carbon chemical shifts are expressed in parts per million (ppm, δ scale) and are referenced to the carbon resonance of the NMR solvent ($CDC1_3$: δ 77.0). Data are represented as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, dd = doublet of doublets, dt = doublet of triplets, td = triplet of doublets, dq= doublet of quartets, dquint = doublet of quintets, sxt = sextet, m = multiplet, br = broad, app = apparent), integration, and coupling constant (J) in Hertz (Hz). Infrared (IR) spectra were obtained using a Shimadzu 8400S FT-IR spectrophotometer referenced to a polystyrene standard. Data are represented as follows: frequency of absorption (cm^{-1}), and intensity of absorption (s = strong, m = medium, br = broad). Gas chromatogram retention times were acquired using a Shimadzu GC-2014 instrument equipped with a Restek Rt-βDEXsm chiral column (30m, 0.25 mm ID, 0.25 μm df). HPLC retention times were acquired using a Beckman System Gold instrument equipped with a Chiracel OD-H column (5 mm particle size, 4.6 mm x 250 mm). Optical rotations were determined using

[48] Kofron, W. G.; Baclawski, L. M. *J. Org. Chem.* **1976**, *41*, 1879–1880.

a JASCO P-2000 digital polarimeter equipped with a sodium lamp source (589 nm). Reported readings are the average of three measurements for each sample. Melting points were determined using a Thomas Scientific capillary melting point apparatus. High-resolution mass spectra were obtained at the Harvard University Mass Spectrometry Facility. X-ray crystallographic analysis was performed at the Harvard University X-Ray Crystallographic Laboratory by Dr. Shao-Liang Zheng.

Effect of formamide source on the formylation of (–)-(1*R*,2*S*)-1,2-diphenylaminoethanol:



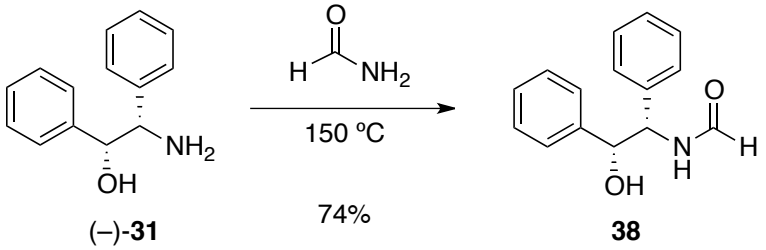
(–)-**31** **38**

97%

***N*-[(1*S*,2*R*)-2-hydroxy-1,2-diphenylethyl]formamide (38)**

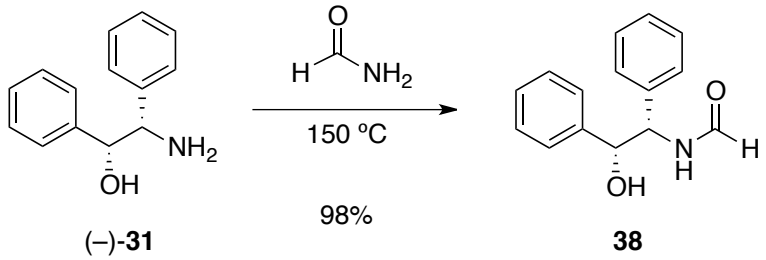
A 1-L round-bottom flask was charged with (–)-(1*R*,2*S*)-2-amino-1,2-diphenylethanol (43.4 g, 203 mmol, 1 equiv), ammonium formate (2.57 g, 40.7 mmol, 0.20 equiv), and formamide (162 mL, 4.07 mol, 20.0 equiv) at 23 ºC. The reaction mixture was warmed to 150 ºC, affording a clear solution. After 2 h, heating was discontinued and the product solution was allowed to cool to 23 ºC, whereupon solidification occurred. The white solid product was suspended in water (200 mL) and the solids were collected by vacuum filtration, rinsing with two 100-mL portions of water. The washed solid was suction-dried for 1 h then was transferred to an empty 2-L round-bottom flask and dried under reduced pressure affording formamide **38** as a white solid (47.5 g, 97%, mp = 198–199 ºC). TLC (80% ethyl acetate–hexanes): R_f = 0.32 (UV, $KMnO_4$). ^{1}H NMR (4.5:1 rotamer ratio, asterisk denotes minor rotamer peaks, 500 MHz, DMSO-d_6), δ: 8.54 (d, 1H, J = 9.5 Hz), 8.15* (t, 1H, 10.8 Hz), 7.89 (s, 1H), 7.73* (d, 1H, J = 11.0 Hz), 7.36-7.19 (m, 10H), 5.52 (d, 1H, J = 4.5 Hz), 5.47* (d, 1H, J = 4.5 Hz), 5.02 (dd, 1H, J = 9.0, 6.5 Hz), 4.77 (app t, 1H, J = 5.5 Hz), 4.71* (dd, 1H, J = 8.0, 4.5 Hz), 4.55* (app t, 1H, J = 9.0 Hz). ^{13}C NMR (6:1 rotamer ratio, asterisk denotes minor rotamer peaks, 125 MHz, DMSO-d_6), δ: 164.1*, 160.0, 142.8*, 142.7, 140.9*, 140.0, 128.2, 127.9*, 127.8*, 127.7*, 127.6, 127.5, 127.2*, 127.0, 126.9*, 126.8, 126.7, 75.5*, 74.9, 61.6*, 56.9. FTIR (neat), cm^{-1}: 3132

(br), 3064, 3030, 1671 (m), 1453 (m). HRMS (ESI): Calcd for $(C_{15}H_{15}NO_2 + H)^+$: 242.1176. Found: 242.1177.



***N*-[(1*S*,2*R*)-2-hydroxy-1,2-diphenylethyl]formamide (38)**

A 1-L round-bottom flask was charged with (–)-(1*R*,2*S*)-2-amino-1,2-diphenylethanol (40.2 g, 189 mmol, 1 equiv) and formamide (150 mL, 3.77 mol, 20.0 equiv) from a fresh bottle (shown by ^{13}C NMR analysis to be pure) at 23 ºC. The reaction mixture was warmed to 150 ºC, resulting in a clear solution that gradually became yellow. After 2.5 h, heating was discontinued and the product solution was allowed to cool to 23 ºC, whereupon solidification occurred. The yellow solid product was suspended in water (200 mL) and the solids were collected by vacuum filtration, rinsing with two 100-mL portions of water. The washed solid was suction-dried for 1 h then was transferred to a flask and dried under reduced pressure. The solid was recrystallized from hot ethanol (90 ºC, 700 mL) to afford formamide **38** as a white solid (33.6 g, 74%).

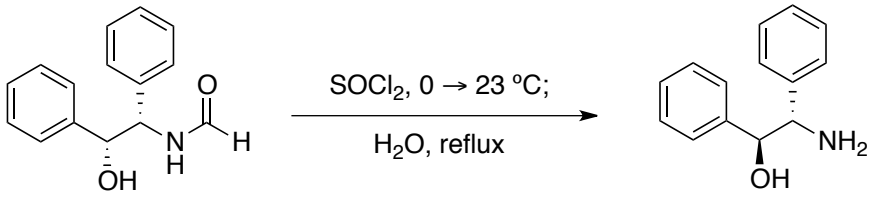


(–)-**31** **38**

***N*-[(1*S*,2*R*)-2-hydroxy-1,2-diphenylethyl]formamide (38)**

A 1-L round-bottom flask was charged with (–)-(1*R*,2*S*)-2-amino-1,2-diphenylethanol (40.7 g, 191 mmol, 1 equiv) and formamide (152 mL, 3.82 mol, 20.0 equiv) from an old bottle (EM Science, shown by ^{13}C NMR analysis to contain a ~5% formate impurity) at 23 ºC. The reaction mixture was warmed to 150 ºC, producing a clear solution. After 3 h, heating was discontinued and the product solution was allowed to cool to 23 ºC, whereupon solidification occurred. The white solid product was suspended in water (200 mL) and the solids were collected by vacuum filtration, rinsing with two 100-mL portions of water. The washed solid was suction-dried for 1 h then was transferred to a flask and dried under reduced pressure affording formamide **38** as a white solid (44.6 g, 98%).

Synthesis of (1S,2S)-pseudoephenamine:

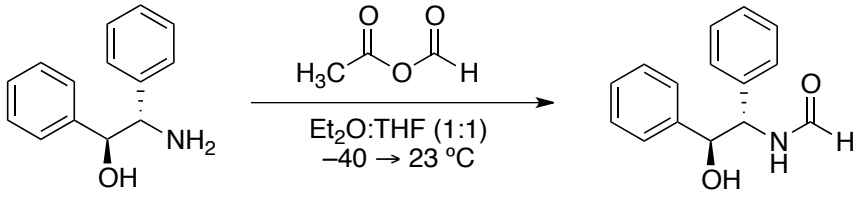


38 92% (–)-**32**

(–)-(1*S*,2*S*)-2-amino-1,2-diphenylethanol [(–)-32]

A 2-L round-bottom flask was charged with formamide **38** (44.6 g, 185 mmol, 1 equiv) then was cooled to 0 ºC. Thionyl chloride (94.0 mL, 1.30 mol, 7.00 equiv) was added and the resulting clear, yellow solution was stirred for 10 min at 0 ºC and for 30 min at 23 ºC. Ice (1070 g) was added slowly (Caution: HCl gas evolution!). A white solid precipitated. After fitting with a reflux condenser the flask was warmed to 120 ºC. The resulting clear solution was stirred for 2 h at 120 ºC. The reaction flask was allowed to cool to 23 ºC, during which time the solution became opaque. Once cool, 5 N aqueous sodium hydroxide solution (1 L) was added to the solution, leading to the precipitation of an off-white solid. The suspension was stirred for 30 min at 23 ºC. The solids were collected by vacuum filtration, rinsing with two 200-mL portions of water. The washed solid was suction-dried for 1 h then was transferred to a 500-mL flask. The solid was dried under reduced pressure. The dried pale-green solid was recrystallized from hot absolute ethanol (140 mL, 80 ºC). A second batch of crystals was collected to give optically pure amino alcohol (–)-**32** was a white, crystalline solid (36.1 g, 92%, mp = 106–108 ºC, $[\alpha]_D^{25}$ = –121.69, *c* 1.12, EtOH). TLC (80% ethyl acetate–hexanes): R_f = 0.13, streak (UV, $KMnO_4$). ^{1}H NMR (600 MHz, $CDCl_3$), δ: 7.12–7.31 (m, 10H), 4.65 (d, 1H, *J* = 6.4 Hz), 3.99 (d, 1H, *J* = 6.4 Hz). ^{13}C NMR (125 MHz, $CDCl_3$), δ: 142.4, 141.7,

128.3, 128.0, 127.3, 127.3, 127.0, 126.5, 78.0, 82.5. FTIR (neat), cm^{-1}: 2928 (m), 2868, 1603, 1493, 1452 (m). HRMS (ESI): Calcd for $(C_{14}H_{15}NO + H)^{+}$: 214.1226. Found: 214.1221.

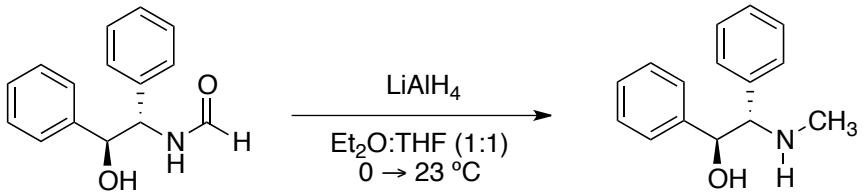


(–)-32 99% **116**

***N*-[(1*S*,2*S*)-2-hydroxy-1,2-diphenylethyl]formamide (116)**

A mixture of acetic anhydride (28.9 mL, 306 mmol, 2.00 equiv) and formic acid (12.9 mL, 337 mmol, 2.10 equiv) was heated for 1 h at 60 ºC then was cooled to 23 ºC. The cooled solution was added by cannula to a solid mixture of (–)-(1*S*,2*S*)-2-amino-1,2-diphenylethanol (32.6 g, 153 mmol, 1 equiv) in a 1:1 mixture of ether (392 mL) and tetrahydrofuran (392 mL) at –40 ºC. The resulting clear, colorless solution was stirred for 45 min at –40 ºC and for 1.75 h at 23 ºC. The reaction mixture was poured into 2 N aqueous sodium hydroxide solution (750 mL), and the layers were separated. The organic layer was washed with 2 N aqueous sodium hydroxide solution (750 mL) and saturated aqueous sodium chloride solution (200 mL). The washed organic layer was dried over magnesium sulfate. The dried solution was filtered, and the filtrate was concentrated to afford formamide **116** as a white solid (36.5 g, 99%, mp = 104-105 ºC). TLC (80% ethyl acetate–hexanes): R_f = 0.36 (UV, $KMnO_4$). ^{1}H NMR (9:1 rotamer ratio, asterisk denotes minor rotamer peaks, 500 MHz, DMSO-d_6), δ: 8.58 (d, 1H, J = 9.3 Hz), 8.17* (t, 1H, J = 10.7 Hz), 7.97 (s, 1H), 7.86* (d, 1H, J = 11.2 Hz), 7.35 (d, 2H, J = 7.8 Hz), 7.33–7.29 (m, 2H), 7.27 (td, 4H, J = 7.3, 3.4 Hz), 7.23–7.12 (m, 3H), 5.62 (m, 1H), 5.03 (dd, 1H, J = 9.3, 3.9 Hz), 4.81 (t, 1H, J = 4.2 Hz), 4.72* (t, 1H, J = 5.6 Hz), 4.58* (dd, 1H, J = 9.8, 6.4 Hz). ^{13}C NMR (8:1 rotamer ratio, asterisk denotes minor rotamer peaks, 125 MHz, DMSO-d_6), δ: 164.6*, 160.7, 143.1, 142.8*, 141.4, 140.6*, 127.9*,

127.8, 127.7*, 127.6, 127.5*, 127.3, 126.9, 126.8*, 126.7, 126.5, 75.7*, 75.1, 62.5*, 57.4. FTIR (neat), cm^{-1}: 3300 (br), 3036, 2876, 1661 (s), 1496 (m). HRMS (ESI): Calcd for $(C_{15}H_{15}NO_2 + Na)^+$: 264.0995. Found: 264.1002.



116 98% (–)-**30**

(–)-(1*S*,2*S*)-pseudoephenamine [(–)-30]

Solid lithium aluminum hydride (11.6 g, 302 mmol, 2.00 equiv) was added carefully in three portions (2.90 g, 2.90 g, 5.90 g; Caution: gas evolution!) to an ice-cooled solution of formamide **116** (36.4 g, 151 mmol, 1 equiv) in a 1:1 mixture of ether (472 mL) and tetrahydrofuran (472 mL). The resulting grey slurry was stirred for 10 min at 0 ºC and for 22 h at 23 ºC. The reaction mixture was cooled to 0 ºC, and excess hydride was quenched by sequential, dropwise addition of water (12 mL), 2 N aqueous sodium hydroxide solution (24 mL), and water (36 mL).[49] The slurry was poured into half-saturated aqueous sodium chloride solution (900 mL), and the layers were separated. The aqueous layer was extracted with two 900-mL portions of ether. The combined organic extracts were dried over magnesium sulfate. The dried solution was filtered, and the filtrate was concentrated to afford (–)-(1*S*,2*S*)-pseudoephenamine as a white solid (33.6 g, 98%, mp = 105–107 ºC, $[\alpha]_D^{25}$ = –104.24, *c* 0.990, EtOH). Recrystallization of the solid product (1.00 g) from hot absolute ethanol yielded large orthorhombic crystals (mp = 109–110 ºC, $[\alpha]_D^{25}$ = –110.5, *c* 1.05, EtOH). TLC (80% ethyl acetate–hexanes): R_f = 0.25 (UV, $KMnO_4$). ^{1}H NMR (600 MHz, $CDCl_3$), δ: 7.25–7.14 (m, 6H), 7.13–7.07 (m, 2H), 7.03 (d, 2H, *J* = 6.7 Hz), 4.57 (d, 1H, *J* = 8.5 Hz), 3.49 (d, 1H, *J* = 8.5 Hz), 2.32 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$), δ: 141.3, 139.5, 128.1, 127.8, 127.3, 127.3, 126.8, 77.7,

[49] Fieser, L. F.; Fieser, M. *Reagents for Organic Synthesis.* **1967**, 581-595.

72.3, 34.2. FTIR (neat), cm^{-1}: 3317, 3065, 3033, 2803, 1453 (m). HRMS (ESI): Calcd for $(C_{15}H_{17}NO + Na)^+$: 250.1202. Found: 250.1205. Anal. Calcd for $C_{15}H_{17}NO$: C, 79.26; H, 7.54; N, 6.16; found: C, 79.28; H, 7.57; N, 6.11.

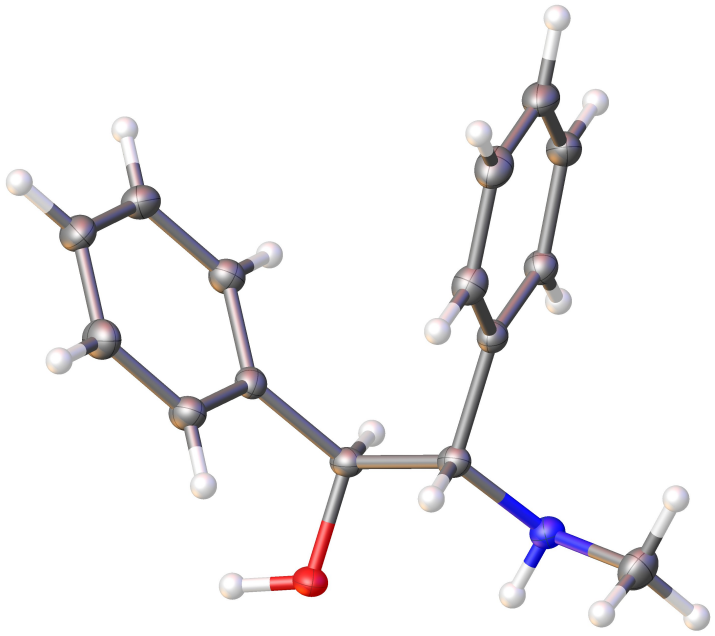


Figure 3.5 X-ray crystal structure of (–)-(1*S*,2*S)*-pseudoephenamine, (–)-**30**.

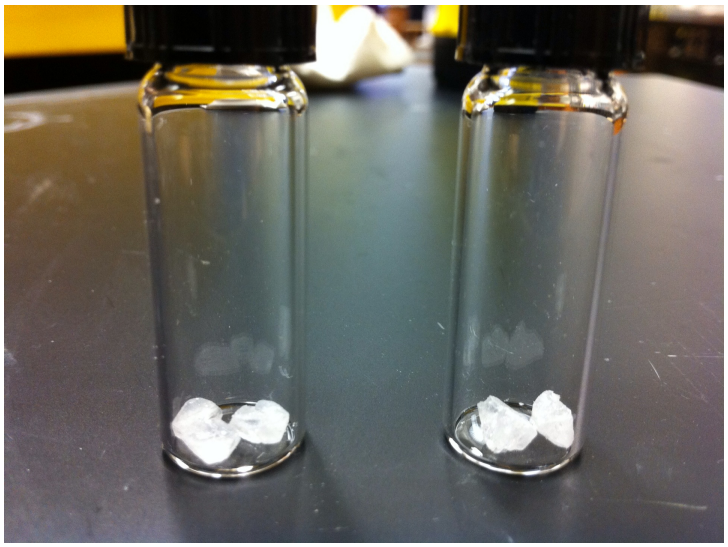
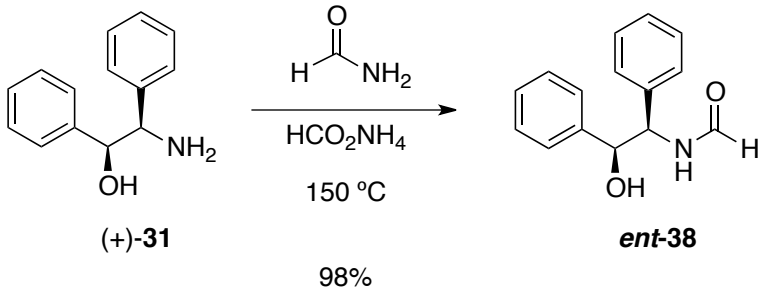


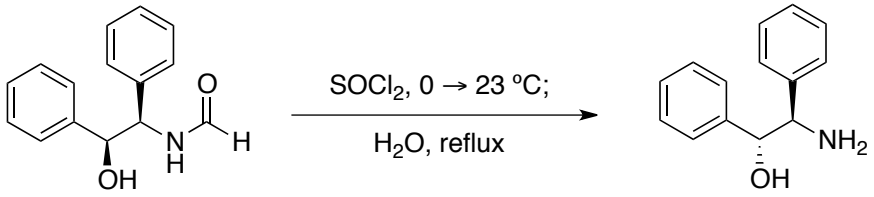
Figure 3.6 Large, orthorhombic crystals of (–)-(1*S*,2*S*)-pseudoephenamine (left) and (+)-(1*R*,2*R*)-pseudoephenamine obtained after recrystallization from hot ethanol.

Synthesis of (1*R*,2*R*)-pseudoephenamine:



***N*-[(1*R*,2*S*)-2-hydroxy-1,2-diphenylethyl]formamide (*ent*-38)**

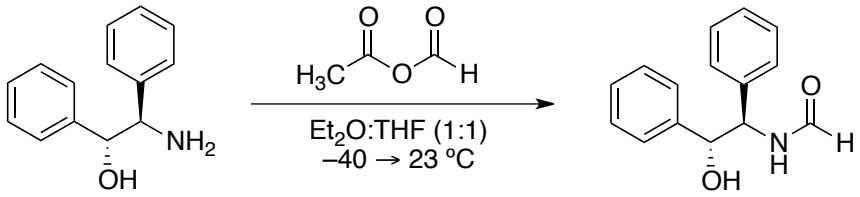
A 500-mL round-bottom flask was charged with (+)-(1*S*,2*R*)-2-amino-1,2-diphenylethanol (30.0 g, 141 mmol, 1 equiv), ammonium formate (1.77 g, 28.1 mmol, 0.20 equiv), and formamide (112 mL, 2.81 mol, 20.0 equiv) at 23 ºC. The reaction mixture was warmed to 150 ºC, affording a clear, pale-yellow solution. After 50 min, heating was discontinued and the product solution was allowed to cool to 23 ºC, whereupon solidification occurred. The white solid product was suspended in water (300 mL) and the solids were collected by vacuum filtration, rinsing with two 200-mL portions of water. The washed solid was suction-dried for 1 h then was transferred to an empty 2-L round-bottom flask and dried under reduced pressure affording formamide ***ent*-38** as a white solid (33.4 g, 98%, mp = 194–196 ºC). The characterization data obtain for formamide ***ent*-38** were identical to those of formamide **38.**



***ent*-38** 92% (+)-**32**

(1R,2R)-(+)-2-amino-1,2-diphenylethanol [(+)-32]

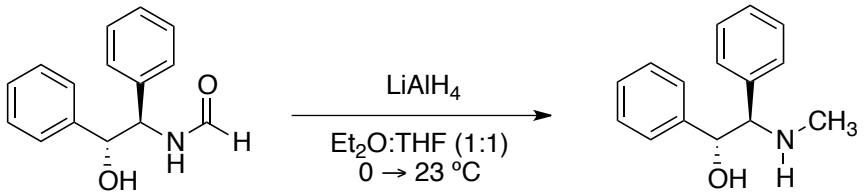
A 2-L round-bottom flask was charged with formamide ***ent*-38** (33.4 g, 138 mmol, 1 equiv) then was cooled to 0 ºC. Thionyl chloride (70.4 mL, 969 mmol, 7.00 equiv) was added and the resulting clear, yellow solution was stirred for 10 min at 0 ºC and for 30 min at 23 ºC. Ice (830 g) was added slowly (Caution: HCl gas evolution!). A white solid precipitated. After fitting with a reflux condenser the flask was warmed to 125 ºC. The resulting clear solution was stirred for 2 h at 125 ºC. The reaction flask was allowed to cool to 23 ºC, during which time the solution became opaque. Once cool, 5 N aqueous sodium hydroxide solution (850 mL) was added to the solution, leading to the precipitation of an off-white solid. The suspension was stirred for 30 min at 23 ºC. The solids were collected by vacuum filtration, rinsing with two 150-mL portions of water. The washed solid was suction-dried for 1 h then was transferred to a 500-mL flask. The solid was dried under reduced pressure. The dried pale-green solid was recrystallized from hot absolute ethanol (120 mL, 80 ºC) to give optically pure amino alcohol (+)-**32** as a white, crystalline solid after two recrystallizations (27.0 g, 92%, mp = 104–106 ºC, $[\alpha]_D^{25}$ = +121.2, *c* 1.15, EtOH). The characterization data obtain for amino alcohol (+)-**32** were identical to those of amino alcohol **32.**



(+)-**32** 99% ***ent*-116**

***N*-[(1*R*,2*R*)-2-hydroxy-1,2-diphenylethyl]formamide (*ent*-116)**

A mixture of acetic anhydride (18.6 mL, 197 mmol, 2.00 equiv) and formic acid (8.31 mL, 217 mmol, 2.10 equiv) was heated for 1 h at 60 ºC then was cooled to 23 ºC. The cooled solution was added by cannula to a solid mixture of (+)-(1*R*,2*R*)-2-amino-1,2-diphenylethanol (21.0 g, 98.0 mmol, 1 equiv) in a 1:1 mixture of ether (490 mL) and tetrahydrofuran (490 mL) at –40 ºC. The resulting clear, colorless solution was stirred for 45 min at –40 ºC and for 1.5 h at 23 ºC. The reaction mixture was poured into 2 N aqueous sodium hydroxide solution (400 mL), and the layers were separated. The organic layer was washed with 2 N aqueous sodium hydroxide solution (400 mL) and saturated aqueous sodium chloride solution (200 mL). The washed organic layer was dried over magnesium sulfate. The dried solution was filtered, and the filtrate was concentrated to afford formamide ***ent*-116** as a white solid (23.6 g, 99%, mp = 101-103 ºC). The characterization data obtain for formamide ***ent*-116** were indentical to those of formamide **116**.

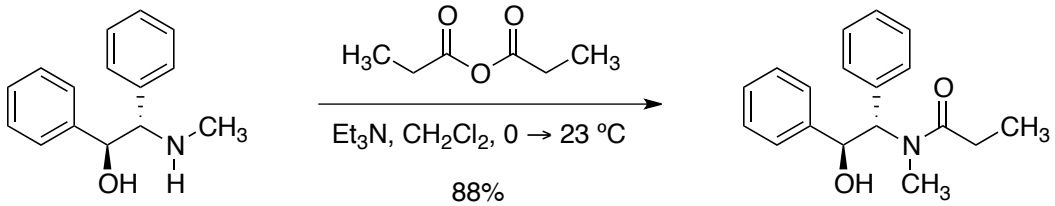


***ent*-116** 97% (+)-**30**

(+)-(1*R*,2*R*)-pseudoephenamine [(+)-30]

Solid lithium aluminum hydride (7.42 g, 196 mmol, 2.00 equiv) was added carefully in three portions (2.00 g, 2.00 g, 3.40 g; Caution: gas evolution!) to an ice-cooled solution of formamide ***ent*-116** (23.6 g, 98.0 mmol, 1 equiv) in a 1:1 mixture of ether (306 mL) and tetrahydrofuran (306 mL). The resulting grey slurry was stirred for 10 min at 0 ºC and for 20.5 h at 23 ºC. The reaction mixture was cooled to 0 ºC, and excess hydride was quenched by sequential, dropwise addition of water (8 mL), 2 N aqueous sodium hydroxide solution (16 mL), and water (24 mL).[48] The slurry was poured into half-saturated aqueous sodium chloride solution (600 mL), and the layers were separated. The aqueous layer was extracted with two 400-mL portions of ether. The combined organic extracts were dried over magnesium sulfate. The dried solution was filtered, and the filtrate was concentrated to afford (+)-(1*R,*2*R*)-pseudoephenamine as a white solid (21.5 g, 97%) Recrystallization of the solid product from hot absolute ethanol (80 ºC, 40 mL) yields large orthorhombic crystals (15.3 g, 71%, mp = 109–110 ºC, $[\alpha]_D^{25}$ = +110.0, *c* 1.15, EtOH). The characterization data obtain for (+)-(*R,R)*-pseudoephenamine were indentical to those of (–)-(1*S*,2*S)*-pseudoephenamine.

Amides depicted in Figure 3.2:



30 **83**

(S,S)-N-(2-hydroxy-1,2-diphenylethyl)-N-methylpropionamide (83)

Propionic anhydride (9.64 mL, 74.8 mmol, 1 equiv) was added to a solution of (–)-(1*S*,2*S*)-pseudoephenamine (17.0 g, 74.8 mmol, 1 equiv) and triethylamine (12.5 mL, 89.8 mmol, 1.20 equiv) in dichloromethane (150 mL) at 0 ºC. The reaction mixture was stirred for 10 min at 0 ºC, then for 35 min at 23 ºC. Excess propionic anhydride was quenched by the addition of water (50 mL). The resulting biphasic mixture was partitioned between water (100 mL) and dichloromethane (650 mL), and the layers were separated. The organic layer was washed sequentially with half-saturated aqueous sodium bicarbonate solution (2 x 100 mL) and 1 N aqueous hydrochloric acid solution (2 x 100 mL). The organic extracts were dried over sodium sulfate. The dried solution was filtered, and the filtrate was concentrated, affording a white solid. Recrystallization of the product from hot toluene (800 mL, 100 ºC) provided the propionamide **83** as a white crystalline solid (18.7 g, 88%, mp = 188-190 ºC). TLC (80% Ethyl acetate–hexanes): R_f = 0.59 (UV, $KMnO_4$). ^{1}H NMR (3:1 rotamer ratio, asterisk denotes minor rotamer peaks, 500 MHz, $CDCl_3$), δ: 7.42-7.16 (m, 10H), 5.64 (d, 1H, *J* = 8.5 Hz), 5.36 (d, 1H, *J* = 8.5 Hz), 5.11* (d, 1H, *J* = 7.5 Hz), 3.89 (br s, 1H), 2.98* (s, 3H), 2.86 (s, 3H), 2.44-2.27 (m, 2H), 1.13 (t, 3H, *J* = 7.7 Hz). ^{13}C NMR (125 MHz, $CDCl_3$), δ: 176.0, 141.8, 137.0, 128.4, 128.4, 128.3, 127.7, 127.5, 126.7, 73.9, 65.9, 34.1, 27.5, 9.2. FTIR (neat), cm^{-1}:

3366 (br), 2940, 1724, 1597 (s), 1454 (m), 1288 (m), 1069 (s). HRMS (ESI): Calcd for $(C_{18}H_{21}NO_2 + Na)^+$: 306.1465. Found: 306.1465.

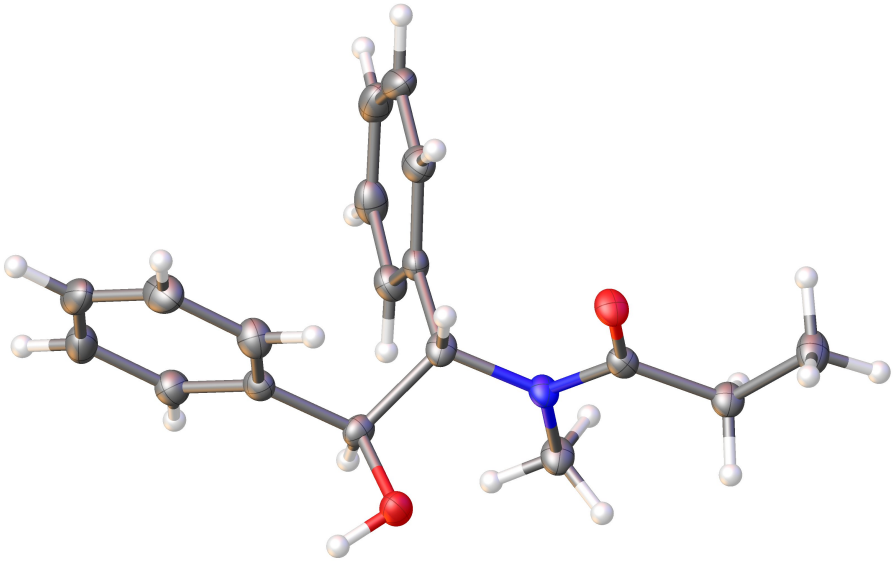
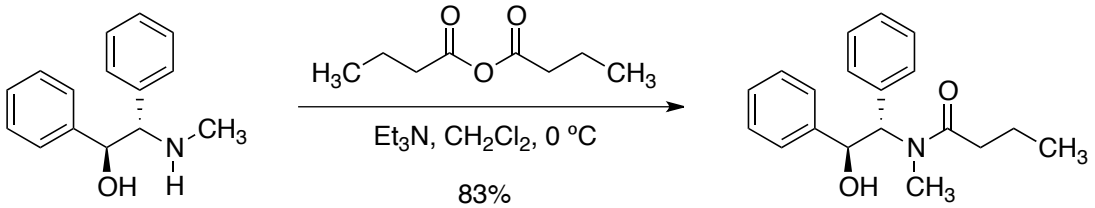


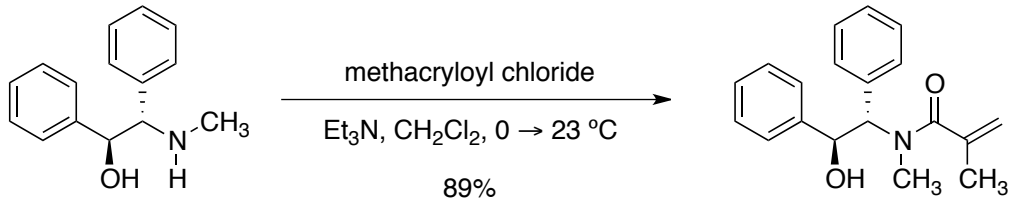
Figure 3.7 X-ray crystal structure of pseudoephenamine propionamide **83**.



30 **84**

***N*-[(1*S*,2*S*)-2-hydroxy-1,2-diphenylethyl]-*N*-methylbutyramide (84)**

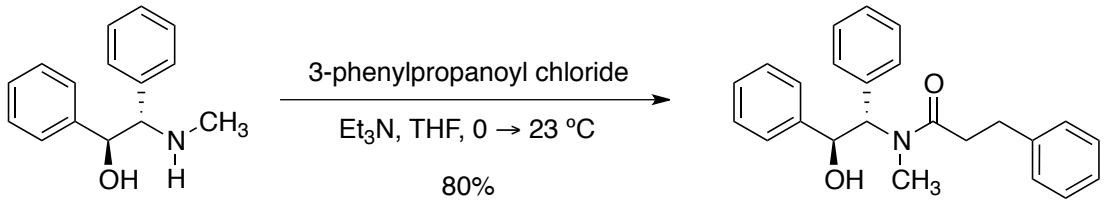
Butyric anhydride (1.2 mL, 7.1 mmol, 1.1 equiv) was added to a solution of (–)-(1*S*,2*S*)-pseudoephenamine (1.5 g, 6.6 mmol, 1 equiv) and triethylamine (1.1 mL, 7.9 mmol, 1.2 equiv) in dichloromethane (13 mL) at 0 ºC. The reaction mixture was stirred for 1 h at 0 ºC. Excess butyric anhydride was quenched by the addition of water (5 mL). The resulting biphasic mixture was partitioned between water (10 mL) and dichloromethane (20 mL), and the layers were separated. The organic layer was washed sequentially with half-saturated aqueous sodium bicarbonate solution (2 x 10 mL) and 1 N aqueous hydrochloric acid solution (2 x 10 mL). The organic extracts were dried over sodium sulfate. The dried solution was filtered, and the filtrate was concentrated, affording a white solid. Recrystallization of the product from hot toluene (14 mL, 100 ºC) provided the butyramide **84** as a white crystalline solid (1.6 g, 83%, mp = 133-135 ºC). TLC (60% Ethyl acetate–hexanes): R_f = 0.45 (UV, $KMnO_4$). ^{1}H NMR (3:1 rotamer ratio, asterisk denotes minor rotamer peaks, 500 MHz, $CDCl_3$), δ: 7.46-7.18 (m, 10H), 5.63 (d, 1H, *J* = 8.0 Hz), 5.40* (d, 1H, *J* = 7.0 Hz), 5.36 (d, 1H, *J* = 8.0 Hz), 5.12* (d, 1H, *J* = 7.5 Hz), 2.96* (s, 3H), 2.86 (s, 3H), 2.37-2.17 (m, 2H), 1.69-1.60 (m, 2H), 0.94 (t, 3H, *J* = 7.5 Hz). ^{13}C NMR (125 MHz, $CDCl_3$), δ: 175.3, 141.9, 137.1, 128.4, 128.38, 128.35, 127.6, 127.5, 126.7, 73.9, 65.9, 36.2, 34.4, 18.4, 13.9. FTIR (neat), cm^{-1}: 3356 (br), 2958, 1616 (m), 1452, 1063, 908 (m). HRMS (ESI): Calcd for $(C_{19}H_{23}NO_2 + Na)^+$: 320.1621. Found: 320.1612.



30 **85**

***N*-[(1*S*,2*S*)-2-hydroxy-1,2-diphenylethyl]-*N*-methylmethacrylamide (85)**

Methacryloyl chloride (946 μL, 9.68 mmol, 1.10 equiv) was added to a solution of (–)-(1*S*,2*S*)-pseudoephenamine (2.00 g, 8.80 mmol, 1 equiv) and triethylamine (1.60 mL, 11.4 mmol, 1.30 equiv) in dichloromethane (22 mL) at 0 ºC. The white suspension was stirred for 5 min at 0 ºC, then for 55 min at 23 ºC. Excess acid chloride was quenched by the addition of water (14 mL). The layers of the resulting biphasic mixture were separated. The aqueous layer was extracted with dichloromethane (3 x 20 mL). The combined organic extracts were dried over sodium sulfate. The dried solution was filtered, and the filtrate was concentrated. The residue was purified by flash column chromatography (10→50% ethyl acetate–hexanes) to provide acrylamide **85** as a white crystalline solid (2.31 g, 89%, mp = 141–143 ºC). TLC (60% ethyl acetate–hexanes): R_f = 0.32 (UV, $KMnO_4$). ^{1}H NMR (2.5:1 rotamer ratio, asterisk denotes minor rotamer peaks, 500 MHz, $CDCl_3$), δ: 7.37–7.49 (m, 2H), 7.16–7.37 (m, 8H), 5.31–5.56 (m, 2H), 5.21* (br s, 1H), 5.14 (br s, 1H), 5.04* (br s, 1H), 4.89 (br s, 1H), 4.29 (d, 1H, *J* = 5.4 Hz), 3.05* (br s, 3H), 2.87 (br s, 3H), 2.26* (br s, 3H), 1.89 (br s, 3H). ^{13}C NMR (3:1 rotamer ratio, asterisk denotes minor rotamer peaks, 125 MHz, $CDCl_3$), δ: 174.3, 141.7, 140.8, 136.6, 128.4, 128.2, 128.1, 127.9*, 127.5, 127.1*, 126.5, 73.6, 72.7*, 66.7*, 65.6, 36.0, 28.7*, 20.9*, 19.8. FTIR (neat), cm^{-1}: 3356 (br), 3032, 1599 (s), 1452 (m), 1087 (m). HRMS (ESI): Calcd for $(C_{19}H_{21}NO_2 + Na)^+$: 318.1465. Found: 318.1460.

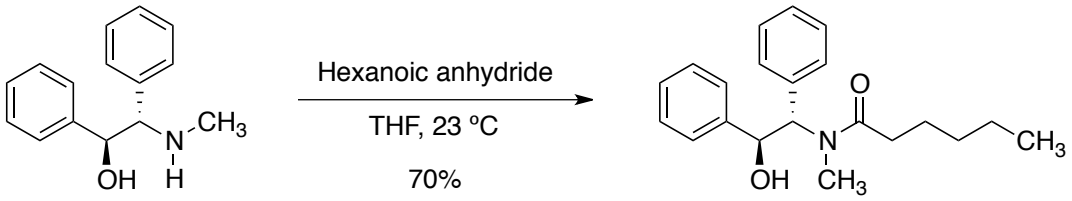


30 **86**

***N*-[(1*S*,2*S*)-2-hydroxy-1,2-diphenylethyl]-*N*-methyl-3-phenylpropanamide (86)**

3-Phenylpropanoyl chloride (6.07 mL, 40.9 mmol, 1.15 equiv) was added dropwise to a solution of (–)-(1*S*,2*S*)-pseudoephenamine (8.08 g, 35.5 mmol, 1 equiv) and triethylamine (6.44 mL, 45.2 mmol, 1.30 equiv) in tetrahydrofuran (85 mL) at 0 ºC. The resulting white suspension was stirred for 10 min at 0 ºC, then for 30 min at 23 ºC. Excess acid chloride was quenched by the addition of water (7 mL). The resulting biphasic mixture was partitioned between ethyl acetate (210 mL) and saturated aqueous sodium chloride solution (70.0 mL), and the layers were separated. The organic layer was washed with saturated aqueous sodium chloride solution (2 x 100 mL). The organic extracts were dried over sodium sulfate. The dried solution was filtered, and the filtrate was concentrated, affording a white solid. Recrystallization of the product from hot toluene (56 mL, 110 ºC) provided the phenylpropanamide **86** as a white crystalline solid (9.51 g, 74%, mp = 147–149 ºC). A second crop was obtained providing an additional 0.77 g of product (80% total yield). TLC (60% ethyl acetate–hexanes): R_f = 0.39 (UV, $KMnO_4$). ^{1}H NMR (5:1 rotamer ratio, asterisk denotes minor rotamer peaks, 500 MHz, $CDCl_3$), δ: 7.36 (d, 2H, *J* = 7.3 Hz), 7.11–7.32 (m, 13H), 5.71 (d, 1H, *J* = 7.8 Hz), 5.29–5.39 (m, 1H), 5.06* (d, 1H, *J* = 7.3 Hz), 3.77 (d, 1H, *J* = 6.4 Hz), 2.89–3.01 (m, 2H), 2.82 (s, 3H), 2.54–2.70 (m, 2H), 2.44–2.53* (m, 2H). ^{13}C NMR (6:1 rotamer ratio, asterisk denotes minor rotamer peaks, 125 MHz, $CDCl_3$), δ: 174.1, 173.2*, 141.7, 141.5*, 141.3*, 141.1, 137.0, 128.5*, 128.4, 128.3, 128.2, 128.2*, 128.1*, 127.6*, 127.6, 127.4, 126.9*, 126.8,

126.0*, 125.9, 73.5, 73.4*, 65.4*, 64.8, 35.9, 35.1*, 33.5, 31.4*, 31.0, 30.0*. FTIR (neat), cm^{-1}: 3385 (br), 3028, 1601 (s), 1452 (m), 1068 (m). HRMS (ESI): Calcd for $(C_{24}H_{25}NO_2 + H)^+$: 360.1958. Found: 360.1954.

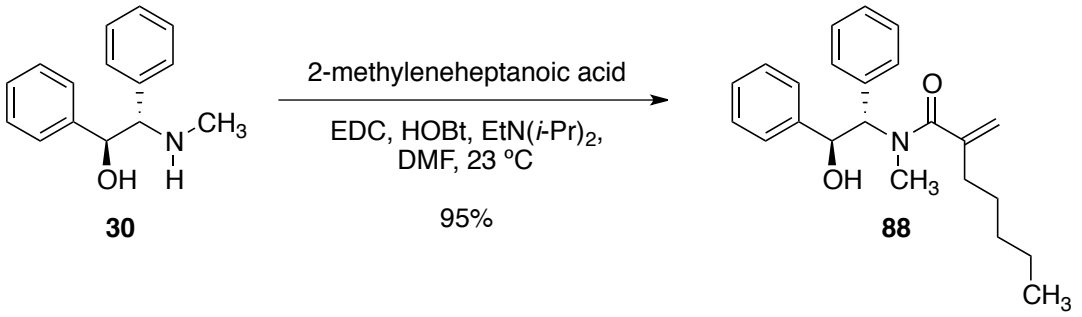


30 **87**

***N*-[(1*S*,2*S*)-2-hydroxy-1,2-diphenylethyl]-*N*-methylhexanamide (87)**

Hexanoic anhydride (7.63 mL, 33.0 mmol, 1.07 equiv) was added to a solution of (–)-(1*S*,2*S*)-pseudoephenamine (7.02 g, 30.9 mmol, 1 equiv) in tetrahydrofuran (64.3 mL) at 23 ºC. The reaction mixture was stirred for 1.5 h at 23 ºC. Excess hexanoic anhydride was quenched by the addition of saturated aqueous sodium bicarbonate solution (39 mL). The resulting biphasic mixture was then partitioned between ethyl acetate (200 mL) and water (140 mL), and the layers were separated. The aqueous layer was extracted with ethyl acetate (2 x 140 mL). The combined organic extracts were dried over sodium sulfate. The dried solution was filtered, and the filtrate was concentrated. Recrystallization of the product from a mixture of hexanes:dichloromethane (8:1, 90 mL, 70 ºC) provided the hexanamide **87** as a white solid (6.32 g, 63%, mp = 88–90 ºC). A second crop was obtained providing an additional 0.75 g of product (70% total yield). TLC (60% ethyl acetate–hexanes): R_f = 0.48 (UV, $KMnO_4$). ^{1}H NMR (6.5:1 rotamer ratio, asterisk denotes minor rotamer peaks, 500 MHz, $CDCl_3$), δ: 7.38 (d, 2H, *J* = 7.8 Hz), 7.17–7.34 (m, 8H), 5.62 (d, 1H, *J* = 7.8 Hz), 5.32–5.42 (m, 1H), 5.12* (d, 1H, *J* = 7.3 Hz), 4.01 (d, 1H, *J* = 5.4 Hz), 2.96* (s, 1H), 2.85 (s, 1H), 2.15–2.39 (m, 2H), 1.49–1.68 (m, 2H), 1.19–1.38 (m, 4H), 0.90 (t, 3H, *J* = 6.8 Hz). ^{13}C NMR (10:1 rotamer ratio, asterisk denotes minor rotamer peaks, 125 MHz, $CDCl_3$), δ: 175.3, 174.3*, 141.8, 141.2*, 137.1, 128.5*, 128.4*, 128.3, 128.2, 128.1*, 127.6*, 127.5, 127.4, 126.9*, 126.7, 73.7, 73.4*, 65.4*, 65.3, 34.1, 34.0*, 33.2*, 31.6*, 31.5, 24.9*, 24.6, 22.4, 13.9. FTIR (neat),

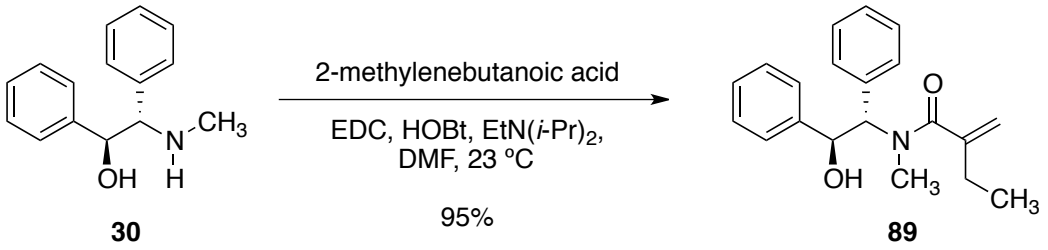
cm^{-1}: 3374 (br), 2957, 1607 (s), 1454 (m), 1063 (m). HRMS (ESI): Calcd for $(C_{21}H_{27}NO_2 + H)^+$: 326.2115. Found: 326.2109.



***N*-[(1*S*,2*S*)-2-hydroxy-1,2-diphenylethyl]-*N*-methyl-2-methyleneheptanamide (88)**

N,*N*-Diisopropylethylamine (2.13 mL, 12.2 mmol, 3.00 equiv), 1-hydroxybenzotriazole hydrate (685 mg, 4.47 mmol, 1.10 equiv), and 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide (858 mg, 4.47 mmol, 1.10 equiv) were added sequentially to a solution of (–)-(1*S*,2*S)*-pseudoephenamine (1.11 g, 4.88 mmol, 1.20 equiv) and 2-methyleneheptanoic acid (785 mg, 7.84 mmol, 1 equiv) in *N*,*N*-dimethylformamide (15.7 mL) at 23 ºC. The resulting yellow solution was stirred for 15 h at 23 ºC. The reaction mixture was partitioned between ethyl acetate (15 mL) and water (40 mL), and the layers were separated. The aqueous layer was extracted with ethyl acetate (2 x 15 mL). The combined organic extracts were washed sequentially with 1 N aqueous hydrochloric acid solution (2 x 20 mL) and half-saturated aqueous sodium chloride solution (2 x 20 mL). The washed organic solution was dried over sodium sulfate. The dried solution was filtered, and the filtrate was concentrated. The residue was purified by flash column chromatography (30→50% ethyl acetate–hexanes) to afford acrylamide **88** as a clear, colorless syrup (1.35 g, 95%). TLC (30% ethyl acetate–hexanes): R_f = 0.21 (UV, $KMnO_4$). ^{1}H NMR (5.2:1 rotamer ratio, asterisk denotes minor rotamer peaks, 500 MHz, $CDCl_3$), δ: 7.43 (d, 2H, *J* = 7.3 Hz), 7.38–7.15 (m, 8H), 5.51 (d, 1H, *J* = 7.5 Hz), 5.43 (t, 1H, *J* = 7.5 Hz), 5.35* (br s, 1H), 5.19* (br s, 1H), 5.13 (br s, 1H), 5.04* (br s, 1H), 4.88 (s, 1H), 4.34 (br d, 1H, *J* = 6.4 Hz), 3.10* (br s, 3H), 2.86 (s, 3H), 2.22 (t, 2H, *J* = 7.6

Hz), 2.11* (br s, 2H), 1.53* (br s, 2H), 1.40 (br s, 2H), 1.30 (br s, 4H), 0.88 (t, 3H, J = 6.4 Hz). ^{13}C NMR (4.5:1 rotamer ratio, asterisk denotes minor rotamer peaks, 125 MHz, $CDCl_3$), δ: 174.1, 174.0*, 145.7*, 145.3, 141.78, 141.3*, 136.9*, 136.7, 128.3, 128.2*, 128.1, 127.8*, 127.4, 127.4, 127.0*, 126.4, 114.1, 113.8*, 73.4, 72.89*, 68.7*, 65.3, 36.1, 33.8, 31.3, 28.9*, 26.9, 22.3, 13.8. FTIR (neat), cm^{-1}: 3378 (br), 2931, 1741, 1602 (s), 1452 (m). HRMS (ESI): Calcd for $(C_{23}H_{29}NO_2 + H)^+$: 352.2271. Found: 352.2279.

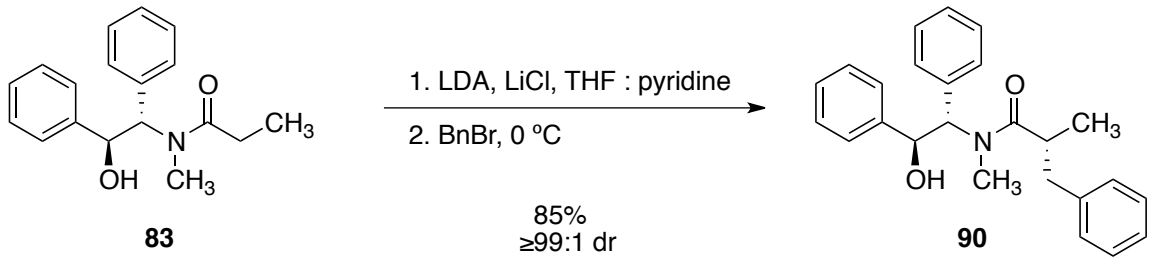


***N*-[(1*S*,2*S*)-2-hydroxy-1,2-diphenylethyl]-*N*-methyl-2-methylenebutanamide (89)**

N,*N*-Diisopropylethylamine (4.11 mL, 23.5 mmol, 3.00 equiv), 1-hydroxybenzotriazole hydrate (1.32 g, 8.62 mmol, 1.10 equiv), and 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide (1.65 g, 8.62 mmol, 1.10 equiv) were added sequentially to a solution of (–)-(1*S*,2*S*)-pseudoephenamine (2.14 g, 9.41 mmol, 1.20 equiv) and 2-methylenebutanoic acid (785 mg, 7.84 mmol, 1 equiv) in *N*,*N*-dimethylformamide (15.7 mL) at 23 ºC. The resulting yellow solution was stirred for 15 h at 23 ºC. The reaction mixture was partitioned between ethyl acetate (15 mL) and water (40 mL), and the layers were separated. The aqueous layer was extracted with ethyl acetate (2 x 15 mL). The combined organic extracts were washed sequentially with 1 N aqueous hydrochloric acid solution (2 x 20 mL) and half-saturated aqueous sodium chloride solution (2 x 20 mL). The washed organic solution was dried over sodium sulfate. The dried solution was filtered, and the filtrate was concentrated. The residue was purified by flash column chromatography (50% ethyl acetate–hexanes) to afford acrylamide **89** as a clear, colorless syrup (2.31 g, 95%). TLC (30% ethyl acetate–hexanes): R_f = 0.12 (UV, $KMnO_4$). ^{1}H NMR (4.5:1 rotamer ratio, asterisk denotes minor rotamer peaks, 500 MHz, $CDCl_3$), δ: 7.43 (d, 2H, *J* = 7.3 Hz), 7.37–7.15 (m, 8H), 5.51 (d, 1H, *J* = 6.8 Hz), 5.43 (t, 1H, *J* = 7.3 Hz), 5.35* (br s, 1H), 5.20* (br s, 1H), 5.13 (br s, 1H), 5.06* (br s, 1H), 4.87 (s, 1H), 4.28 (br d, 1H, *J* = 6.4 Hz), 3.09* (br s, 3H), 2.86 (s, 3H), 2.17–2.38 (m, 2H), 2.10* (br s, 2H), 1.13* (br s, 3H), 1.03 (t, 3H, *J* = 7.3 Hz). ^{13}C NMR (2.5:1 rotamer ratio, asterisk denotes

minor rotamer peaks, 125 MHz, $CDCl_3$), δ: 173.9, 146.7*, 146.3, 141.7, 141.5*, 136.6*, 136.7, 128.1, 128.0, 127.9, 127.4*, 127.3*, 127.3*, 127.2, 126.9, 126.8*, 126.3, 73.0, 72.3*, 66.7*, 64.1, 35.3, 28.7*, 26.4, 26.3*, 11.3. FTIR (neat), cm^{-1}: 3373 (br), 2923, 1739, 1602 (s), 1451 (m). HRMS (ESI): Calcd for $(C_{20}H_{23}NO_2 + H)^+$: 310.1802. Found: 310.1812.

Synthesis of α,α-disubstituted pseudoephenamine amides depicted in Table 3.1:



(*R*)-*N*-[(1*S*,2*S*)-2-hydroxy-1,2-diphenylethyl]-*N*,2-dimethyl-3-phenylpropanamide (90)

N,*N*-Diisopropylamine (5.59 mL, 39.9 mmol, 2.26 equiv) was added by syringe to a stirring suspension of lithium chloride (4.49 g, 106 mmol, 6.00 equiv) in tetrahydrofuran (40 mL) at 23 ºC. The resulting slurry was cooled to –78 ºC. A freshly titrated solution of *n*-butyllithium in hexanes (2.40 M, 16.3 mL, 2.21 equiv) was added by syringe. The reaction mixture was warmed briefly to 0 ºC (5 min), then was cooled to –78 ºC. An ice-cooled solution of amide **83** (5.00 g, 17.6 mmol, 1 equiv) in pyridine (44 mL) was added by cannula. The transfer was quantitated with tetrahydrofuran (5 mL). The reaction mixture was stirred for 1 h at –78 ºC, for 15 min at 0 ºC, and for 5 min at 23 ºC, then was cooled to 0 ºC, whereupon benzyl bromide (3.14 mL, 26.5 mmol, 1.50 equiv) was added. After 30 min, saturated aqueous ammonium chloride solution (1.5 mL) was added to the ice-cold product mixture. The biphasic mixture was partitioned between ethyl acetate (130 mL) and a 1:1 mixture of saturated aqueous sodium chloride solution and 1 N aqueous hydrochloric acid solution (160 mL). The layers were separated. The aqueous layer was extracted with two 80-mL portions of ethyl acetate. The combined organic extracts were washed with water (100 mL). The washed organic solution was dried over sodium sulfate. The dried solution was filtered and the filtrate was concentrated. The

residue was purified by flash column chromatography (10→70% ethyl acetate–hexanes) to provide amide **90** as a pale-orange solid (6.36 g, 97%). The purified product was recrystallized from toluene (25 mL, 100 ºC) affording a white crystalline solid (5.08 g, 77%, mp = 128-129 ºC). A second crop was obtained providing an additional 0.55 g of product (85% total yield). The product **90** (26.0 mg, 0.07 mmol, 1 equiv) was silylated with a mixture of chlorotrimethylsilane (24.7 μL, 0.19 mmol, 2.80 equiv) and triethylamine (34.9 μL, 0.25 mmol, 3.60 equiv) in dichloromethane (1 mL) at 23 ºC for 10 min, and chiral HPLC analysis of the resulting trimethylsilyl ether established that amide **90** was of ≥99:1 dr (Chiralcel OD-H, 95:5 hexanes:*i*-PrOH, 1 mL/min, λ = 220 nm, t_R (minor, amide **96**) = 5.82 min, t_R (major, amide **90**) = 7.28 min). This diastereomeric ratio was confirmed by ^{1}H NMR analysis of the corresponding oxazolinium triflate (see below). TLC (60% Ethyl acetate–hexanes): R_f = 0.56 (UV, $KMnO_4$). ^{1}H NMR (3:1 rotamer ratio, asterisk denotes minor rotamer peaks, 500 MHz, $CDCl_3$), δ: 7.44-6.98 (m, 15H), 5.68 (d, 1H, *J* = 7.0 Hz), 5.35 (t, 1H, *J* = 7.0 Hz), 5.21* (dd, 1H, *J* = 7.5, 3.5 Hz), 5.02* (d, 1H, *J* = 8.5 Hz), 3.58 (br s, 1H), 3.12-3.04* (m, 1H), 3.03-2.88 (m, 2H), 2.70 (s, 3H), 2.62 (dd, 1H, *J* = 12.0, 5.0 Hz), 1.09 (d, 3H, *J* = 6.5 Hz), 1.05* (d, 3H, *J* = 6.5 Hz). ^{13}C NMR (125 MHz, $CDCl_3$), δ: 177.9, 141.7, 140.0, 136.9, 129.0, 128.4 (2), 128.3, 128.2, 127.6, 127.3, 126.6, 126.1, 73.7, 64.5, 40.2, 38.8, 33.9, 17.6. FTIR (neat), cm^{-1}: 3371 (br), 3028, 1618 (s), 1452, 1080, 908 (s). HRMS (ESI): Calcd for $(C_{25}H_{27}NO_2 + H)^+$: 374.2115. Found: 374.2116.

Assignment of absolute stereochemistry of α-tertiary alkylation product established by X-ray crystallographic analysis:

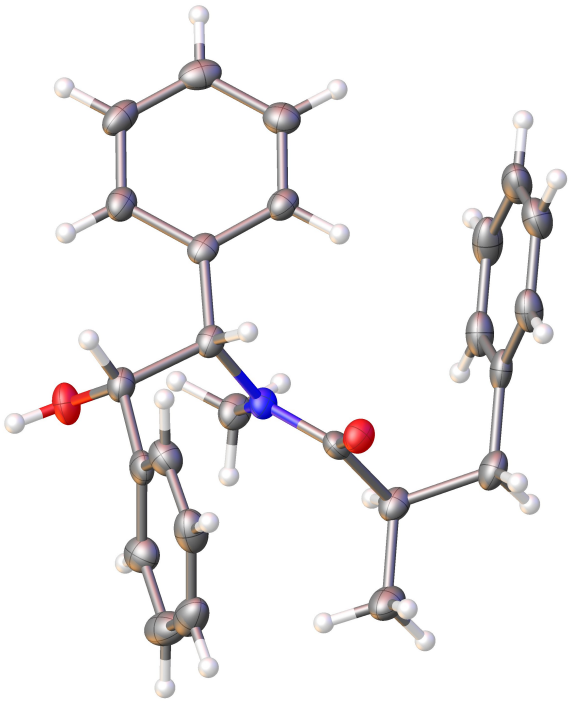
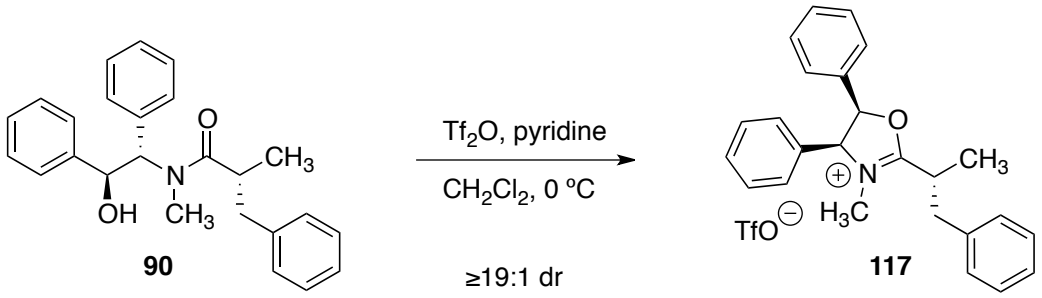
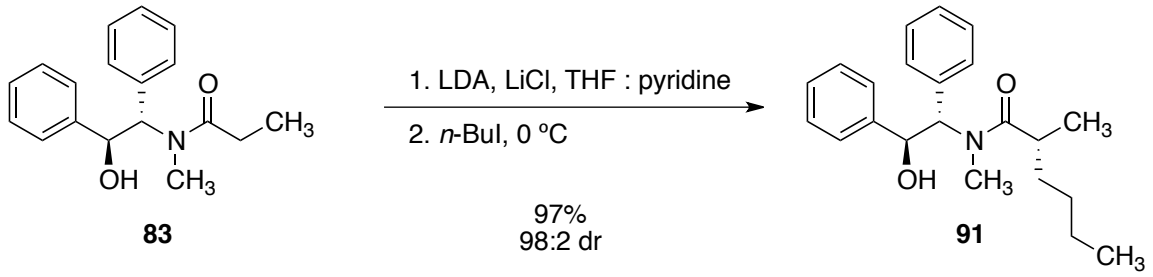


Figure 3.8 X-ray crystal structure of α-tertiary pseudoephenamine amide **90**.



Cyclic oxazolinium triflate (117)

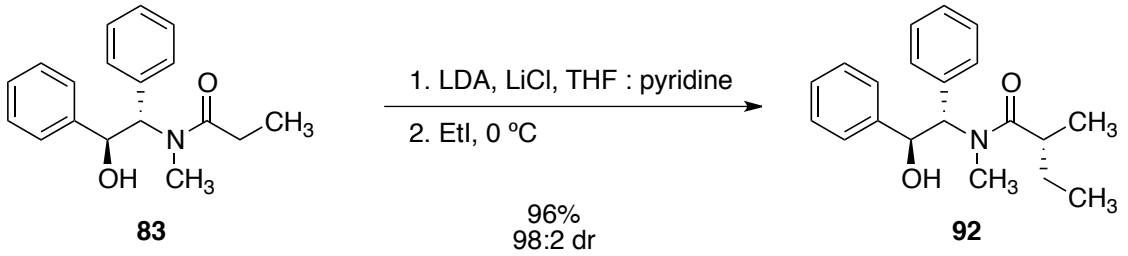
Trifluoromethanesulfonic anhydride (18.9 μL, 0.112 mmol, 2.00 equiv) was added dropwise by syringe to a stirring solution of the α-tertiary amide **90** (21.0 mg, 0.056 mmol, 1 equiv) and pyridine (13.6 μL, 0.169 mmol, 3.00 equiv) in dichloromethane (2 mL) at 0 °C. The reaction mixture was stirred for 10 min at 0 °C. The product solution was concentrated by rotary evaporation at ~40 mmHg, then with a vacuum manifold at 0.1 mmHg for 3 h. The diastereomeric ratio of the residue was determined to be ≥19:1 by ^{1}H NMR analysis. ^{1}H NMR (≥19:1 diastereomeric ratio, asterisk denotes pyridinium ion peaks, 500 MHz, $CDCl_3$), δ: 8.90* (t, 1H, *J* = 6.0 Hz), 8.55* (t, 1H, *J* = 7.75 Hz), 8.06* (t, 1H, *J* = 6.5 Hz), 7.41-6.83 (m, 15H), 6.03 (d, 1H, *J* = 11.0 Hz), 3.55-3.47 (m, 2H), 3.23 (s, 3H), 2.95 (dd, 1H, *J* = 8.5, 4.5 Hz), 1.56 (d, 3H, *J* = 7.0 Hz).



(*R*)-*N*-[(1*S*,2*S*)-2-hydroxy-1,2-diphenylethyl]-*N*,2-dimethylhexanamide (91)

N,*N*-Diisopropylamine (3.35 mL, 23.9 mmol, 2.26 equiv) was added by syringe to a stirring suspension of lithium chloride (2.69 g, 63.5 mmol, 6.00 equiv) in tetrahydrofuran (26 mL) at 23 ºC. The resulting slurry was cooled to –78 ºC. A freshly titrated solution of *n*-butyllithium in hexanes (2.50 M, 9.36 mL, 2.21 equiv) was added by syringe. The reaction mixture was warmed briefly to 0 ºC (5 min), then was cooled to –78 ºC. An ice-cooled solution of amide **83** (3.00 g, 10.6 mmol, 1 equiv) in pyridine (23 mL) was added by cannula. The transfer was quantitated with tetrahydrofuran (5 mL). The reaction mixture was stirred for 1 h at –78 ºC, for 15 min at 0 ºC, and for 5 min at 23 ºC, then was cooled to 0 ºC, whereupon 1-iodobutane (3.01 mL, 26.5 mmol, 2.50 equiv) was added. After 1.2 h, aqueous ammonium chloride solution (1.5 mL) was added to the ice-cold product mixture. The biphasic mixture was partitioned between ethyl acetate (80 mL) and a 1:1 mixture of saturated aqueous sodium chloride solution and 1 N aqueous hydrochloric acid solution (100 mL). The layers were separated. The aqueous layer was extracted with two 50-mL portions of ethyl acetate. The combined organic extracts were washed with water (60 mL). The washed organic solution was dried over sodium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue was purified by flash column chromatography (30→50% ethyl acetate–hexanes) to provide amide **91** as a pale-yellow oil, which solidified upon standing after 4-5 days (3.49 g,

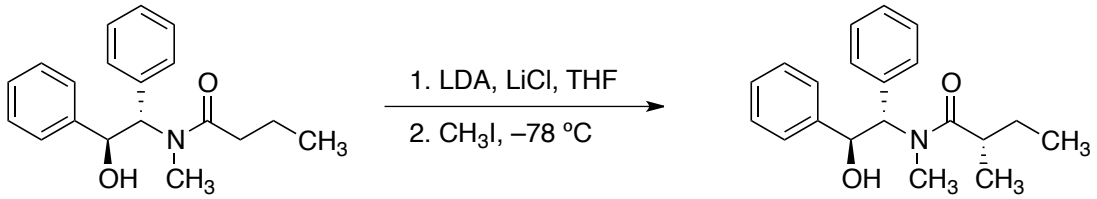
97%). The diastereomeric ratio of the purified product was determined to be 98:2 dr by chiral HPLC analysis (Chiralcel OD-H, 95:5 hexanes:*i*-PrOH, 1 mL/min, λ = 220 nm, t_R (major, amide **91**) = 16.5 min, t_R (minor, amide **95**) = 21.8 min). TLC (60% Ethyl acetate–hexanes): R_f = 0.64 (UV, $KMnO_4$). ^{1}H NMR (3:1 rotamer ratio, asterisk denotes minor rotamer peaks, 500 MHz, $CDCl_3$), δ: 7.45-7.19 (m, 10H), 5.61 (d, 1H, *J* = 8.0 Hz), 5.53* (d, 1H, *J* = 7.5 Hz), 5.38 (t, 1H, *J* = 7.2 Hz), 5.22* (d, 1H, *J* = 8.0 Hz), 4.32* (br s, 1H), 4.22 (d, 1H, *J* = 6.0 Hz), 3.01* (s, 3H), 2.88 (s, 3H), 2.64 (sxt, 1H, *J* = 6.9 Hz), 1.66-1.58 (m, 1H), 1.36-1.22 (m, 3H), 1.21-1.13 (m, 2H), 1.07 (d, 3H, *J* = 7.0 Hz), 1.03* (d, 3H, *J* = 7.0 Hz), 0.87 (t, 3H, *J* = 7.2 Hz). ^{13}C NMR (125 MHz, $CDCl_3$), δ: 179.1, 142.0, 137.2, 128.4, 128.3, 128.2, 127.5, 127.4, 126.6, 73.8, 66.2, 36.5, 34.7, 33.7, 29.6, 22.2, 17.3, 13.9. FTIR (neat), cm^{-1}: 3365 (br), 2930, 1618 (s), 1452, 1069. HRMS (ESI): Calcd for $(C_{22}H_{29}NO_2 + H)^+$: 340.2271. Found: 340.2274.



(*R*)-*N*-[(1*S*,2*S*)-2-hydroxy-1,2-diphenylethyl]-*N*,2-dimethylbutanamide (92)

N,*N*-Diisopropylamine (3.35 mL, 23.9 mmol, 2.26 equiv) was added by syringe to a stirring suspension of lithium chloride (2.69 g, 63.5 mmol, 6.00 equiv) in tetrahydrofuran (21 mL) at 23 ºC. The resulting slurry was cooled to –78 ºC. A freshly titrated solution of *n*-butyllithium in hexanes (2.50 M, 9.36 mL, 2.21 equiv) was added by syringe. The reaction mixture was warmed briefly to 0 ºC (5 min), then was cooled to –78 ºC. An ice-cooled solution of amide **83** (3.00 g, 10.6 mmol, 1 equiv) in pyridine (26 mL) was added by cannula. The transfer was quantitated with tetrahydrofuran (5 mL). The reaction mixture was stirred for 1 h at –78 ºC, for 15 min at 0 ºC, and for 5 min at 23 ºC, then was cooled to 0 ºC, whereupon iodoethane (2.13 mL, 26.5 mmol, 2.50 equiv) was added. After 55 min, aqueous ammonium chloride solution (1.5 mL) was added to the ice-cold product mixture. The biphasic mixture was partitioned between ethyl acetate (80 mL) and a 1:1 mixture of saturated aqueous sodium chloride solution and 1 N aqueous hydrochloric acid solution (100 mL). The layers were separated. The aqueous layer was extracted with two 50-mL portions of ethyl acetate. The combined organic extracts were washed with water (60 mL). The washed organic solution was dried over sodium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue was purified by flash column chromatography (30→50% ethyl acetate–hexanes) to provide amide **92** as a pale-yellow oil, which solidified upon standing after 3-4 days (3.15 g,

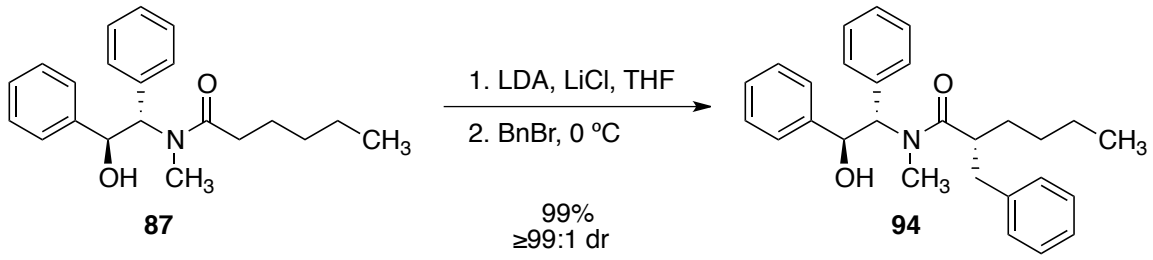
96%). The diastereomeric ratio of the purified product was determined to be 98:2 dr by chiral HPLC analysis (Chiralcel OD-H, 95:5 hexanes:*i*-PrOH, 1 mL/min, λ = 220 nm, t_R (major, amide **92**) = 20.7 min, t_R (minor, amide **93**) = 24.9 min). TLC (60% Ethyl acetate–hexanes): R_f = 0.50 (UV, $KMnO_4$). ^{1}H NMR (3:1 rotamer ratio, asterisk denotes minor rotamer peaks, 500 MHz, $CDCl_3$), δ: 7.46-7.16 (m, 10H), 5.66 (d, 1H, *J* = 8.0 Hz), 5.55* (d, 1H, *J* = 8.0 Hz), 5.38 (d, 1H, *J* = 7.5 Hz), 5.22* (d, 1H, *J* = 7.0 Hz), 4.32* (br s, 1H), 4.12 (br s, 1H), 3.00* (s, 3H), 2.89 (s, 3H), 2.58 (sxt, 1H, *J* = 6.8 Hz), 1.75-1.61 (m, 1H), 1.43-1.32 (m, 1H), 1.08 (d, 3H, *J* = 7.0 Hz), 1.03* (d, 3H, *J* = 6.5 Hz), 0.84 (t, 3H, *J* = 7.5 Hz). ^{13}C NMR (125 MHz, $CDCl_3$), δ: 178.9, 141.9, 137.2, 128.5, 128.3, 128.2, 127.6, 127.5, 126.6, 73.8, 65.9, 38.2, 34.5, 26.9, 17.0, 11.9. FTIR (neat), cm^{-1}: 3379 (br), 2967, 1616 (s), 1452, 1082, 908 (s). HRMS (ESI): Calcd for $(C_{20}H_{25}NO_2 + H)^+$: 312.1958. Found: 312.1964.



(*S*)-*N*-[(1*S*,2*S*)-2-hydroxy-1,2-diphenylethyl]-*N*,2-dimethylbutanamide (93)

N,*N*-Diisopropylamine (1.07 mL, 7.57 mmol, 2.25 equiv) was added by syringe to a stirring suspension of lithium chloride (0.86 g, 20.2 mmol, 6.00 equiv) in tetrahydrofuran (10 mL) at 23 ºC. The resulting slurry was cooled to –78 ºC. A freshly titrated solution of *n*-butyllithium in hexanes (2.40 M, 2.80 mL, 2.00 equiv) was added by syringe. The reaction mixture was warmed briefly to 0 ºC (5 min), then was cooled to –78 ºC. An ice-cooled solution of amide **84** (1.00 g, 3.36 mmol, 1 equiv) in tetrahydronfuran (12 mL) was added by cannula. The transfer was quantitated with tetrahydrofuran (2 mL). The reaction mixture was stirred for 1 h at –78 ºC, for 15 min at 0 ºC, and for 5 min at 23 ºC, then was cooled to 0 ºC, whereupon iodomethane (0.63 mL, 10.1 mmol, 3.00 equiv) was added. After 1 h, aqueous ammonium chloride solution (2 mL) was added to the ice-cold product mixture. The biphasic mixture was partitioned between ethyl acetate (20 mL) and a 1:1 mixture of saturated aqueous sodium chloride solution and 1 N aqueous hydrochloric acid solution (30 mL). The layers were separated. The aqueous layer was extracted with two 20-mL portions of ethyl acetate. The combined organic extracts were dried over sodium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue was purified by flash column chromatography (30→40% ethyl acetate–hexanes) to provide amide **93** as a white solid (0.91 g, 87%, mp = 89-90 ºC). The diastereomeric ratio of the purified product was determined to be ≥99:1 dr by chiral

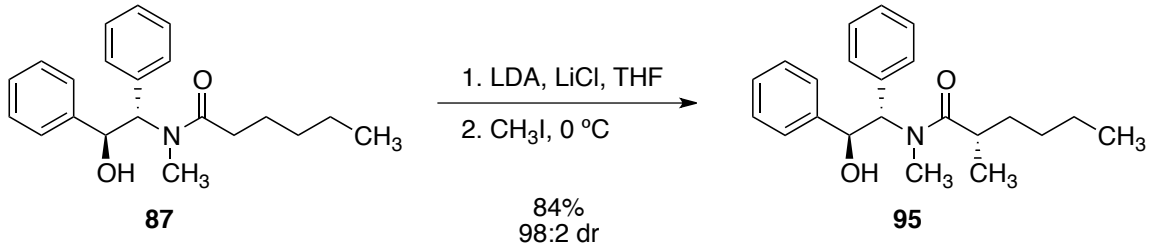
HPLC analysis (Chiralcel OD-H, 95:5 hexanes:*i*-PrOH, 1 mL/min, λ = 220 nm, t_R (minor, amide **92**) = 21.1 min, t_R (major, amide **93**) = 25.3 min). TLC (60% Ethyl acetate–hexanes): R_f = 0.63 (UV, $KMnO_4$). ^{1}H NMR (3:1 rotamer ratio, asterisk denotes minor rotamer peaks, 500 MHz, $CDCl_3$), δ: 7.46-7.18 (m, 10H), 5.54 (d, 1H, *J* = 7.5 Hz), 5.40 (d, 1H, *J* = 7.0 Hz), 5.21* (d, 1H, *J* = 7.5 Hz), 4.31 (br s, 1H), 3.02* (s, 3H), 2.87 (s, 3H), 2.57 (sxt, 1H, *J* = 6.8 Hz), 1.81-1.63 (m, 1H), 1.45-1.30 (m, 1H), 1.03 (d, 3H, *J* = 6.5 Hz), 0.84 (t, 3H, *J* = 7.7 Hz), 0.79 (t, 3H, *J* = 7.2 Hz). ^{13}C NMR (125 MHz, $CDCl_3$), δ: 178.9, 142.0, 137.2, 128.4, 128.3, 128.2, 127.5, 127.4, 126.6, 73.9, 66.7, 38.3, 35.1, 26.9, 17.1, 11.9. FTIR (neat), cm^{-1}: 3363 (br), 2965, 1616 (s), 1450, 1082, 910. HRMS (ESI): Calcd for $(C_{20}H_{25}NO_2 + H)^+$: 312.1958. Found: 312.1969.



(*R*)-2-benzyl-*N*-[(1S,2*S*)-2-hydroxy-1,2-diphenylethyl]-*N*-methylhexanamide (94)

N,*N*-Diisopropylamine (2.97 mL, 20.8 mmol, 2.26 equiv) was added by syringe to a stirring suspension of lithium chloride (2.35 g, 55.3 mmol, 6.00 equiv) in tetrahydrofuran (20 mL) at 23 ºC. The resulting slurry was cooled to –78 ºC. A freshly titrated solution of *n*-butyllithium in hexanes (2.53 M, 8.05 mL, 2.21 equiv) was added by syringe. The reaction mixture was warmed briefly to 0 ºC (5 min) before cooling to –78 ºC. An ice-cooled solution of amide **87** (3.00 g, 9.22 mmol, 1 equiv) in tetrahydrofuran (20 mL with 6.1 mL rinse) was added via cannula. The reaction mixture was stirred for 1 h at –78 ºC, for 15 min at 0 ºC, and for 5 min at 23 ºC, then was cooled to 0 ºC, whereupon benzyl bromide (1.65 mL, 13.8 mmol, 1.50 equiv) was added. After 1.3 h, saturated aqueous ammonium chloride solution (2 mL) was added to the ice-cold product mixture. The resulting biphasic mixture was partitioned between ethyl acetate (80 mL) and a 1:1 mixture of saturated aqueous sodium chloride solution and 1 N aqueous hydrochloric acid solution (100 mL). The layers were separated. The aqueous layer was extracted with two 60-mL portions of ethyl acetate. The combined organic extracts were dried over sodium sulfate. The dried solution was filtered, and the filtrate was concentrated. The residue was recrystallized from hot ethyl acetate–hexanes (1:1, 10 mL, 70 ºC) to provide amide **94** as a white crystalline solid (3.35 g, 88%, mp = 112–114 ºC). A second crop was obtained providing an additional 0.47 g of amide **94** (99% total yield). The

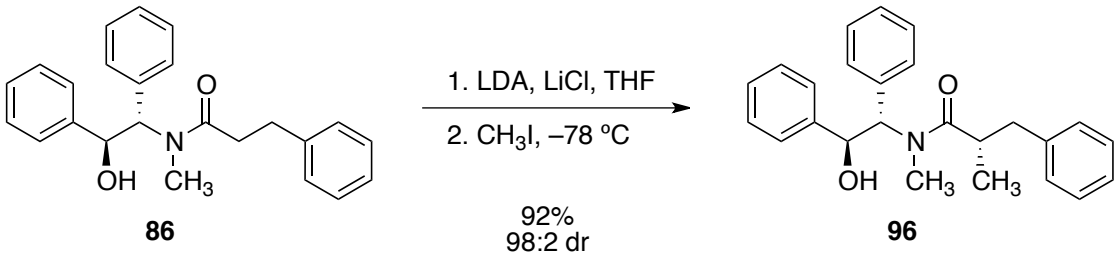
diastereomeric ratio of the purified product was determined to be ≥99:1 by chiral HPLC analysis (Chiralcel OD-H, 95:5 hexanes:*i*-PrOH, 1 mL/min, λ = 220 nm, t_R(major, amide **94**) = 25.1 min, t_R(minor, amide **97**) = not observed). TLC (50% ethyl acetate–hexanes): R_f = 0.57 (UV, $KMnO_4$). ^{1}H NMR (12:1 rotamer ratio, asterisk denotes minor rotamer peaks, 500 MHz, $CDCl_3$), δ: 7.39* (m, 2H), 7.35 (d, 2H, *J* = 7.3 Hz), 7.3* (m, 2H), 7.23–7.28 (m, 2H), 7.10–7.22 (m, 9H), 6.97–7.03 (m, 2H), 6.90–6.96* (m, 2H), 5.79 (d, 1H, *J* = 7.6 Hz), 5.31 (t, 1H, *J* = 7.2 Hz), 4.97* (dd, 1H, *J* = 9.1, 4.9 Hz), 4.73* (d, 1H, *J* = 9.4 Hz), 3.42 (br s, 1H), 3.15* (s, 3H), 2.92–3.00 (m, 1H), 2.85–2.92 (m, 1H), 2.72 (dd, 1H, *J* = 13.0, 4.8 Hz), 2.64 (s, 3H), 1.60–1.71 (m, 1H), 1.41–1.50 (m, 1H), 1.14–1.33 (m, 4H), 0.87 (t, 3H, *J* = 7.2 Hz), 0.66* (t, 3H, *J* = 7.2 Hz). ^{13}C NMR (10:1 rotamer ratio, asterisk denotes minor rotamer peaks, 125 MHz, $CDCl_3$), δ: 177.3, 176.9*, 141.7, 140.8*, 140.5*, 139.9*, 137.8*, 136.9, 129.2*, 128.9, 128.5*, 128.3, 128.2, 128.19, 127.9*, 127.8*, 127.5*, 127.4, 127.1, 127.0*, 126.6, 126.3*, 125.9, 73.9*, 73.3, 66.7*, 63.2, 47.6*, 44.2, 39.3*, 39.0, 33.2, 32.8, 32.6*, 29.9*, 29.4*, 29.2, 22.7, 22.6*, 13.8, 13.7*. FTIR (neat), cm^{-1}: 3356 (br), 2929, 1616 (s), 1446 (m). HRMS (ESI): Calcd for $(C_{28}H_{33}NO_2 + H)^+$: 416.2584. Found: 416.2580.



(*S*)-*N*-[(1*S*,2*S*)-2-hydroxy-1,2-diphenylethyl]-*N*,2-dimethylhexanamide (95)

N,*N*-Diisopropylamine (3.02 mL, 21.2 mmol, 2.26 equiv) was added by syringe to a stirring suspension of lithium chloride (2.38 g, 56.2 mmol, 6.00 equiv) in tetrahydrofuran (20 mL) at 23 ºC. The resulting slurry was cooled to –78 ºC. A freshly titrated solution of *n*-butyllithium in hexanes (2.53 M, 8.19 mL, 2.21 equiv) was added by syringe. The reaction mixture was warmed briefly to 0 ºC (5 min) before cooling to –78 ºC. An ice-cooled solution of amide **87** (3.05 g, 9.37 mmol, 1 equiv) in tetrahydrofuran (20 mL with 6.9 mL rinse) was added by cannula. The reaction mixture was stirred for 1 h at –78 ºC, for 15 min at 0 ºC, and for 5 min at 23 ºC, then was cooled to 0 ºC, whereupon iodomethane (2.34 mL, 37.5 mmol, 4.00 equiv) was added. After 40 min, saturated aqueous ammonium chloride solution (2 mL) was added to the ice-cold product mixture. The resulting biphasic mixture was partitioned between ethyl acetate (80 mL) and a 1:1 mixture of saturated aqueous sodium chloride solution and 1 N aqueous hydrochloric acid solution (100 mL). The layers were separated. The aqueous layer was extracted with two 60-mL portions of ethyl acetate. The combined organic extracts were dried over sodium sulfate. The dried solution was filtered, and the filtrate was concentrated. The residue was purified by flash column chromatography (5→40% ethyl acetate–hexanes) to provide amide **95** as an off-white solid (2.86 g, 90%). The diastereomeric ratio of the purified product was determined to be 95:5 by chiral HPLC analysis (Chiralcel OD-H, 95:5 hexanes:*i*-PrOH, 1 mL/min, λ = 220 nm, t_R(minor) = 16.3 min, t_R(major) = 20.0

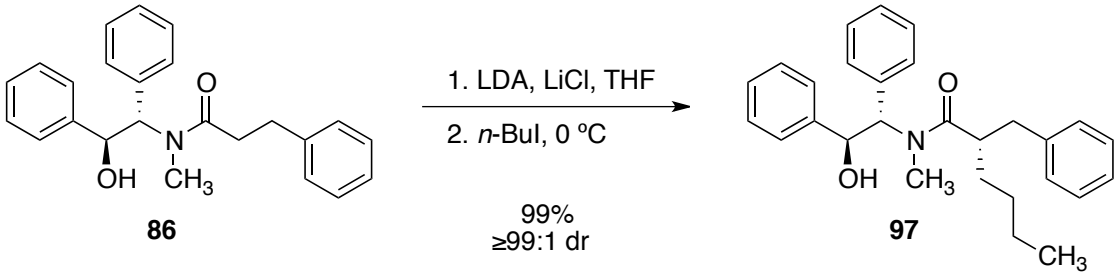
min). The purified product was recrystallized from hot ether–hexanes (1:7, 10 mL, 40 ºC) to provide amide **95** as an off-white crystalline solid (2.42 g, 76%, mp = 77–79 ºC). A second crop was obtained providing an additional 0.26 g of amide XX (84% total yield). The diastereomeric ratio of the recrystallized product was determined to be 98:2 by chiral HPLC analysis (Chiralcel OD-H, 95:5 hexanes:*i*-PrOH, 1 mL/min, λ = 220 nm, t_R(minor, amide **91**) = 17.2 min, t_R(major, amide **95**) = 21.6 min). TLC (30% ethyl acetate–benzene): R_f = 0.45 (UV, $KMnO_4$). ^{1}H NMR (10:1 rotamer ratio, asterisk denotes minor rotamer peaks, 500 MHz, $CDCl_3$), δ: 7.40 (d, 2H, *J* = 7.6 Hz), 7.19–7.36 (m, 8H), 5.53 (d, 1H, *J* = 7.0 Hz), 5.34-5.44 (m, 1H), 5.19* (d, 1H, *J* = 7.3 Hz), 4.36 (br s, 1H), 3.02* (s, 3H), 2.87 (s, 3H), 2.63 (sxt, 1H, *J* = 6.7 Hz), 1.59–1.70 (m, 1H), 1.22–1.39 (m, 3H), 1.10–1.22 (m, 2H), 1.07* (d, 3H, *J* = 6.7 Hz), 1.03 (d, 3H, *J* = 6.7 Hz), 0.87 (t, 3H, *J* = 7.3 Hz), 0.80* (t, 3H, *J* = 6.9 Hz). ^{13}C NMR (10:1 rotamer ratio, asterisk denotes minor rotamer peaks, 125 MHz, $CDCl_3$), δ: 178.7, 1778.1*, 141.9, 141.4*, 137.4*, 137.3, 128.3*, 128.2, 128.1, 128.1*, 128.0, 127.9*, 127.5*, 127.3, 127.2, 126.9*, 126.4, 73.6, 73.3*, 65.8, 65.4*, 36.3, 35.6*, 34.8, 34.1*, 33.4, 30.1*, 29.4, 22.6, 22.5*, 17.3*, 17.2, 13.9, 13.8*. FTIR (neat), cm^{-1}: 3354 (br), 2931, 1618 (s), 1450 (m). HRMS (ESI): Calcd for $(C_{22}H_{29}NO_2 + H)^+$: 340.2271. Found: 340.2261.



(*S*)-*N*-[(1*S*,2*S*)-2-hydroxy-1,2-diphenylethyl]-*N*,2-dimethyl-3-phenylpropanamide (96)

N,*N*-Diisopropylamine (1.76 mL, 12.4 mmol, 2.26 equiv) was added by syringe to a stirring suspension of lithium chloride (1.39 g, 32.8 mmol, 6.00 equiv) in tetrahydrofuran (10 mL) at 23 ºC. The resulting slurry was cooled to –78 ºC. A freshly titrated solution of *n*-butyllithium in hexanes (2.46 M, 4.92 mL, 2.21 equiv) was added by syringe. The reaction mixture was warmed briefly to 0 ºC (5 min) before cooling to –78 ºC. An ice-cooled solution of amide **86** (1.97 g, 5.47 mmol, 1 equiv) in tetrahydrofuran (13 mL with 4.0 mL rinse) was added by cannula. The reaction mixture was stirred for 1 h at –78 ºC, for 15 min at 0 ºC, and for 5 min at 23 ºC, then was cooled to 0 ºC, whereupon iodomethane (1.37 mL, 19.5 mmol, 2.50 equiv) was added. After 2 h, saturated aqueous ammonium chloride solution (2 mL) was added to the ice-cold product mixture. The resulting biphasic mixture was partitioned between ethyl acetate (80 mL) and a 1:1 mixture of saturated aqueous sodium chloride solution and 1 N aqueous hydrochloric acid solution (100 mL). The layers were separated. The aqueous layer was extracted with two 60-mL portions of ethyl acetate. The combined organic extracts were dried over sodium sulfate. The dried solution was filtered, and the filtrate was concentrated. The residue was purified by flash column chromatography (5→50% ethyl acetate–hexanes) to provide amide **96** as a white solid (1.88 g, 92%). The product **96** (21.1 mg, 0.06 mmol, 1

equiv) was silylated with a mixture of chlorotrimethylsilane (20.2 μL, 0.16 mmol, 2.80 equiv) and triethylamine (28.3 μL, 0.20 mmol, 3.60 equiv) in dichloromethane (1 mL) at 23 ºC for 10 min, and chiral HPLC analysis of the resulting trimethylsilyl ether established that amide **96** was of 98:2 dr (Chiralcel OD-H, 95:5 hexanes:*i*-PrOH, 1 mL/min, λ = 220 nm, t_R (minor, amide **90**) = 5.82 min, t_R (major, amide **96**) = 7.28 min). TLC (30% ethyl acetate–hexanes) R_f = 0.41 (UV, $KMnO_4$). ^{1}H NMR (6:1 rotamer ratio, asterisk denotes minor rotamer peaks, 500 MHz, $CDCl_3$), δ: 7.43 (d, 2H, *J* = 7.3 Hz), 7.33 (t, 4H, *J* = 7.8 Hz), 7.13–7.30 (m, 9H), 6.82* (d, 2H, *J* = 7.3 Hz), 5.49 (d, 1H, *J* = 7.3 Hz), 5.32–5.41 (m, 1H), 5.19* (d, 1H, *J* = 7.6 Hz), 4.52 (d, 1H, *J* = 5.3 Hz), 3.07–3.19* (m, 2H), 2.98–3.06 (m, 2H), 2.94* (s, 3H), 2.82 (s, 3H), 2.61–2.71 (m, 1H), 1.09 (d, 3H, *J* = 6.4 Hz). ^{13}C NMR (10:1 rotamer ratio, asterisk denotes minor rotamer peaks, 125 MHz, $CDCl_3$), δ: 177.9, 177.2*, 141.7, 141.4*, 140.2*, 139.8, 136.9*, 136.8, 129.0*, 128.9, 128.5*, 128.3, 128.2, 128.17*, 128.1, 128.0*, 127.9*, 127.9, 127.3, 127.3*, 127.2, 127.0*, 126.5, 126.1, 126.0*, 73.5, 72.9*, 67.0, 65.2*, 40.9*, 39.7, 38.8, 38.4*, 35.0, 17.9*, 17.3. FTIR (neat), cm^{-1}: 3360 (br), 3028, 1620 (s), 1452 (m). HRMS (ESI): Calcd for $(C_{25}H_{27}NO_2 + H)^+$: 374.2115. Found: 374.2105.

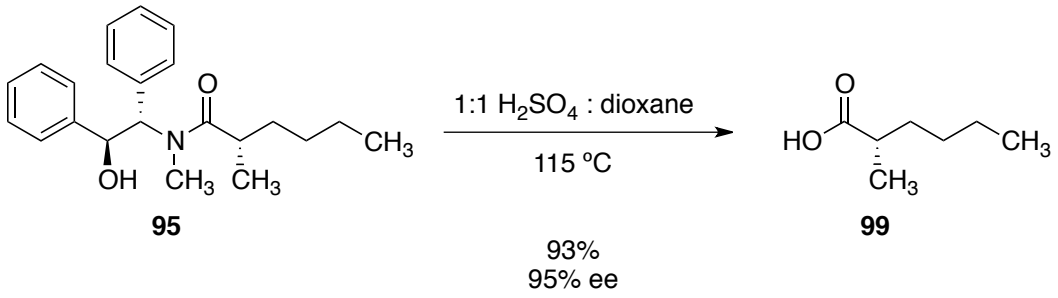


(*S*)-2-benzyl-*N*-[(1*S*,2*S*)-2-hydroxy-1,2-diphenylethyl]-*N*-methylhexanamide (97)

N,*N*-Diisopropylamine (2.51 mL, 17.6 mmol, 2.26 equiv) was added by syringe to a stirring suspension of lithium chloride (1.98 g, 46.7 mmol, 6.00 equiv) in tetrahydrofuran (20 mL) at 23 ºC. The resulting slurry was cooled to –78 ºC. A freshly titrated solution of *n*-butyllithium in hexanes (2.53 M, 6.80 mL, 2.21 equiv) was added by syringe. The reaction mixture was warmed briefly to 0 ºC (5 min) before cooling to –78 ºC. An ice-cooled solution of amide **86** (2.80 g, 7.79 mmol, 1 equiv) in tetrahydrofuran (13 mL with 5.9 mL rinse) was added by cannula. The reaction mixture was stirred for 1 h at –78 ºC, for 15 min at 0 ºC, and for 5 min at 23 ºC, then was cooled to –78 ºC, whereupon 1-iodobutane (2.22 mL, 19.5 mmol, 2.50 equiv) was added, and the reaction mixture was warmed to 0 ºC. After 3 h, saturated aqueous ammonium chloride solution (2 mL) was added to the ice-cold product mixture. The resulting biphasic mixture was partitioned between ethyl acetate (80 mL) and a 1:1 mixture of saturated aqueous sodium chloride solution and 1 N aqueous hydrochloric acid solution (100 mL). The layers were separated. The aqueous layer was extracted with two 60-mL portions of ethyl acetate. The combined organic extracts were dried over sodium sulfate. The dried solution was filtered, and the filtrate was concentrated. The residue was purified by flash column chromatography (5→40% ethyl acetate–hexanes) to provide amide **97** as a white solid (3.20 g, 99%, mp = 109–111 ºC). The diastereomeric ratio of the purified product was

determined to be ≥99:1 by chiral HPLC analysis (Chiralcel OD-H, 95:5 hexanes:*i*-PrOH, 1 mL/min, λ = 220 nm, t_R(major, amide **97**) = 5.73 min, t_R(minor, amide **94**) = 7.32 min). TLC (50% ethyl acetate–benzene): R_f = 0.41 (UV, $KMnO_4$). ^{1}H NMR (10:1 rotamer ratio, asterisk denotes minor rotamer peaks, 500 MHz, $CDCl_3$), δ: 7.37 (d, 2H, *J* = 7.6 Hz), 7.23–7.31 (m, 4H), 7.05–7.23 (m, 9H), 7.03* (d, 1H, *J* = 6.7 Hz), 6.70* (d,, 1H, *J* = 7.6 Hz), 5.58 (d, 1H, *J* = 8.20 Hz), 5.18–5.28 (m, 1H), 5.15 (d, 1H, *J* = 8.5 Hz), 3.87 (br s, 1H), 2.98* (s, 3H), 2.89–2.96 (m, 2H), 2.64–2.76 (m, 4H), 1.54–1.67 (m, 1H), 1.38–1.49 (m, 1H), 1.28–1.38* (m, 2H), 1.17–1.28 (m, 2H), 1.07–1.16 (m, 2H), 0.91* (t, 3H, *J* = 7.0 Hz), 0.82 (t, 3H, *J* = 7.3 Hz). ^{13}C NMR (10:1 rotamer ratio, asterisk denotes minor rotamer peaks, 125 MHz, $CDCl_3$), δ: 177.6, 176.8*, 141.6, 141.1*, 140.3*, 139.9, 136.9*, 136.82, 129.0*, 128.9, 128.5*, 128.4, 128.2, 128.2, 128.1, 128.1*, 127.9*, 127.4, 127.28, 127.1*, 126.7, 126.2, 125.9*, 73.4*, 73.3*, 66.4, 65.6*, 44.6, 44.2*, 38.8, 38.5*, 34.3, 32.7, 32.2*, 29.7*, 29.4, 22.9*, 22.7, 14.0*, 13.8. FTIR (neat), cm^{-1}: 3362 (br), 2929, 1620 (s), 1452 (m). HRMS (ESI): Calcd for $(C_{28}H_{33}NO_2 + H)^+$: 416.2584. Found: 416.2576.

Acidic hydrolysis to form carboxylic acids:



95 **99**

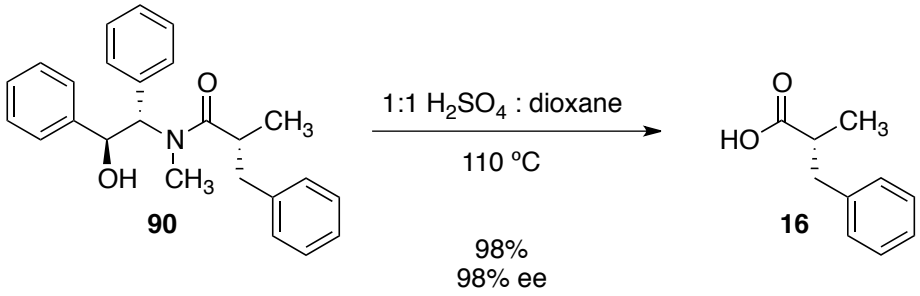
93%
95% ee

(*S*)-2-methylhexanoic acid (99)

A biphasic solution of amide **95** (213 mg, 0.629 mmol, 1 equiv) in 1,4-dioxane (1.0 mL) and 9 N aqueous sulfuric acid solution (1.0 mL) was heated for 6 h at 115 ºC and then cooled to 0 ºC. The pH of the mixture was adjusted to pH ≥ 10 by the slow addition of 5 N aqueous sodium hydroxide solution, and the resulting mixture was partitioned between water (10 mL) and dichloromethane (20 mL). The layers were separated. The aqueous layer was extracted with dichloromethane (2 x 20 mL). The aqueous layer was acidified to pH ≤ 1 by the slow addition of 9 N aqueous sulfuric acid solution. The resulting acidic aqueous layer was extracted with dichloromethane (3 x 20 mL). The latter organic extracts were combined and dried over anhydrous sodium sulfate. The dried solution was filtered, and the filtrate was concentrated to afford acid **99** as a clear liquid (75.9 mg, 93%). Coupling of acid **99** (32.8 mg, 0.252 mmol, 1 equiv) with (*R*)-(α-methylbenzyl)amine (38.5 μL, 0.302 mmol, 1.20 equiv) in the presence of 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride (72.4 mg, 0.378 mmol, 1.50 equiv), 1-hydroxybenzotriazole hydrate (57.9 mg, 0.378 mmol, 1.50 equiv), and triethylamine (140 μL, 1.01 mmol, 4.00 equiv) in *N*,*N*-dimethyformamide (500 μL) at 23 ºC for 20 h gave the corresponding (*R*)-(α-methylbenzyl)amide which was analyzed by chiral capillary GC to establish an ee of 97% for acid **99** (Restek Rt-βDEXsm column, 30

m, 0.23 mmID, oven temperature 190 ºC, t_R(minor) = 5.57 min, t_R(major) = 5.91 min). The characterization data obtained for acid **99** were in agreement with values previously reported.[50]

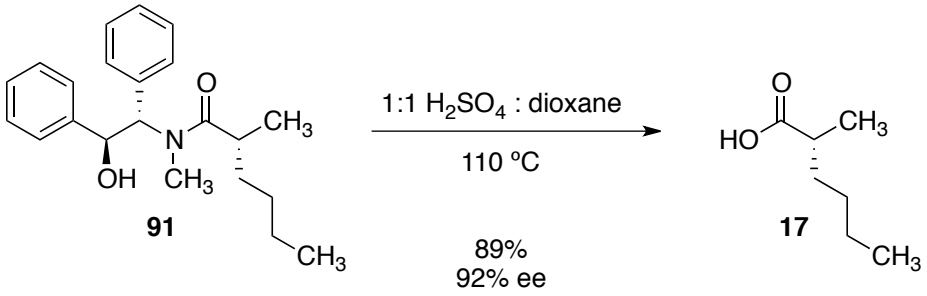
[50] Myers, A. G.; Yang, B. H.; Chen, H.; McKinstry, L.; Kopecky, D. J.; Gleason, J. L. *J. Am. Chem. Soc.* **1997**, *119*, 6496–6511.



(*R*)-2-methyl-3-phenylpropanoic acid (16)

A biphasic solution of amide **90** (500 mg, 1.34 mmol, 1 equiv) in dioxane (2.1 mL) and 9 N aqueous sulfuric acid solution (2.1 mL) was heated for 5.3 h at 115 ºC and then cooled to 0 ºC. The pH of the mixture was adjusted to pH ≥ 10 by the slow addition of 5 N aqueous sodium hydroxide solution, and the resulting mixture was partitioned between water (10 mL) and dichloromethane (20 mL). The layers were separated. The aqueous layer was extracted with dichloromethane (2 x 20 mL). The aqueous layer was acidified to pH ≤ 1 by the slow addition of 9 N aqueous sulfuric acid solution. The resulting acidic aqueous layer was extracted with dichloromethane (3 x 20 mL). The latter organic extracts were combined and dried over sodium sulfate. The dried solution was filtered, and the filtrate was concentrated to afford acid **16** as a clear liquid (216 mg, 98%). Coupling of acid **16** (25.0 mg, 0.152 mmol, 1 equiv) with (*R*)-(α-methylbenzyl)amine (23.0 μL, 0.183 mmol, 1.20 equiv) in the presence of 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride (43.8 mg, 0.228 mmol, 1.50 equiv), 1-hydroxybenzotriazole hydrate (30.9 mg, 0.228 mmol, 1.50 equiv), and triethylamine (85.0 μL, 0.609 mmol, 4.00 equiv) in *N*,*N*-dimethylformamide (500 μL) at 23 ºC for 20 h gave the corresponding (*R*)-(α-methylbenzyl)amide which was analyzed by chiral capillary GC to establish an ee of 98% for acid **16** (Restek Rt-βDEXsm column, 30 m, 0.23 mmID, oven temperature 190 ºC, t_R (major) = 22.0 min, t_R (minor) = 24.8 min). The

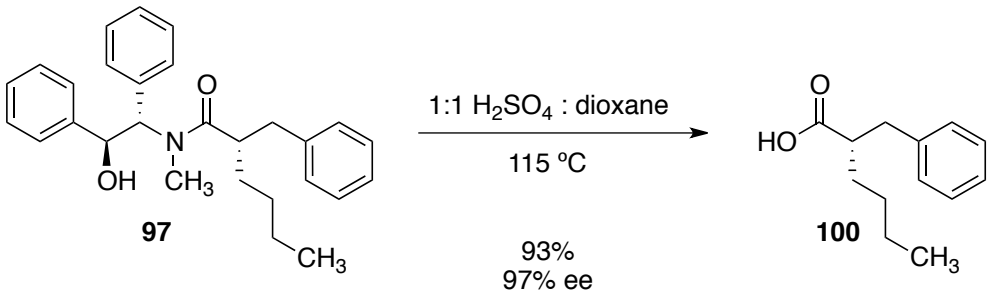
characterization data obtained for acid **16** were in agreement with values previously reported.[50]



(*R*)-2-methylhexanoic acid (17)

A biphasic solution of amide **91** (250 mg, 0.736 mmol, 1 equiv) in dioxane (1.2 mL) and 9 N aqueous sulfuric acid solution (1.2 mL) was heated for 5.5 h at 110 ºC and then cooled to 0 ºC. The pH of the mixture was adjusted to pH ≥ 10 by the slow addition of 5 N aqueous sodium hydroxide solution, and the resulting mixture was partitioned between water (10 mL) and dichloromethane (20 mL). The layers were separated. The aqueous layer was extracted with dichloromethane (2 x 20 mL). The aqueous layer was acidified to pH ≤ 1 by the slow addition of 9 N aqueous sulfuric acid solution. The resulting acidic aqueous layer was extracted with dichloromethane (3 x 20 mL). The latter organic extracts were combined and dried over sodium sulfate. The dried solution was filtered, and the filtrate was concentrated to afford acid **17** as a clear liquid (85.0 mg, 89%). Coupling of acid **17** (25.0 mg, 0.192 mmol, 1 equiv) with (*R*)-(α-methylbenzyl)amine (29.3 μL, 0.230 mmol, 1.20 equiv) in the presence of 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride (55.2 mg, 0.288 mmol, 1.50 equiv), 1-hydroxybenzotriazole hydrate (38.9 mg, 0.288 mmol, 1.50 equiv), and triethylamine (107 μL, 0.768 mmol, 4.00 equiv) in *N*,*N*-dimethylformamide (640 μL) at 23 ºC for 20 h gave the corresponding (*R*)-(α-methylbenzyl)amide which was analyzed by chiral capillary GC to establish an ee of 92% for acid **17** (Restek Rt-βDEXsm column, 30 m, 0.23 mmID, oven temperature 190 ºC, t_R (minor) = 5.6 min, t_R (major) = 5.9 min). The

characterization data obtained for acid **17** were in agreement with values previously reported.[50]

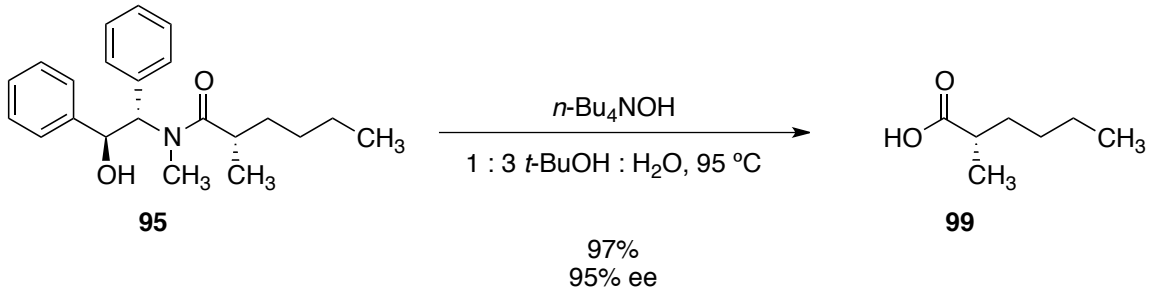


(*S*)-2-benzylhexanoic acid (100)

A biphasic solution of amide **97** (198 mg, 0.476 mmol, 1 equiv) in 1,4-dioxane (1.0 mL) and 9 N aqueous sulfuric acid solution (1.0 mL) was heated for 9 h at 115 ºC and then cooled to 0 ºC. The pH of the mixture was adjusted to pH ≥ 10 by the slow addition of 5 N aqueous sodium hydroxide solution, and the resulting mixture was partitioned between water (10 mL) and dichloromethane (20 mL). The layers were separated. The aqueous layer was extracted with dichloromethane (2 x 20 mL). The aqueous layer was acidified to pH ≤ 1 by the slow addition of 9 N aqueous sulfuric acid solution. The resulting acidic aqueous layer was extracted with dichloromethane (3 x 20 mL). The latter organic extracts were combined and dried over anhydrous sodium sulfate. The dried solution was filtered, and the filtrate was concentrated to afford acid **100** as a clear liquid (91.0 mg, 93%). Coupling of acid **100** (24.7 mg, 0.120 mmol, 1 equiv) with (*R*)-(α-methylbenzyl)amine (18.3 μL, 0.144 mmol, 1.20 equiv) in the presence of 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride (34.4 mg, 0.180 mmol, 1.50 equiv), 1-hydroxybenzotriazole hydrate (27.5 mg, 0.180 mmol, 1.50 equiv), and triethylamine (66.8 μL, 0.479 mmol, 4.00 equiv) in *N*,*N*-dimethyformamide (500 μL) at 23 ºC for 20 h gave the corresponding (*R*)-(α-methylbenzyl)amide, which was analyzed by chiral capillary GC to establish an ee of 97% for acid **100** (Restek Rt-βDEXsm column, 30 m, 0.23 mmID, oven temperature 190 ºC, t_R(minor) = 45.8 min, t_R(major) =

47.9 min). The characterization data obtained for acid **100** were in agreement with values previously reported.[50]

Basic hydrolysis to form carboxylic acids:



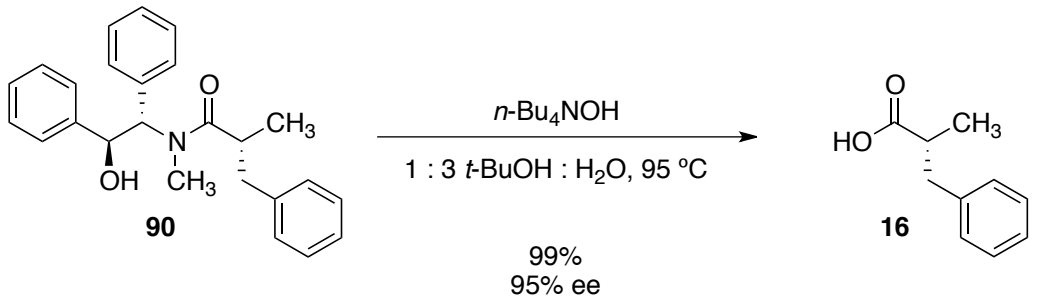
95 **99**

97%
95% ee

(*S*)-2-methylhexanoic acid (99)

An aqueous solution of tetra-*n*-butylammonium hydroxide (40% w/w, 4.84 mL, 7.39 mmol, 5.00 equiv) was added in one portion to a stirring biphasic solution of amide **95** (501 mg, 1.48 mmol, 1 equiv) and in *tert*-butyl alcohol (5.5 mL) and water (16.5 mL). The resulting biphasic mixture was stirred for 24 h at 95 ºC and then cooled to 23 ºC. The biphasic mixture was partitioned between 0.5 N aqueous sodium hydroxide solution (200 mL) and ether (30 mL). The layers were separated. The aqueous layer was extracted with two 30-mL portions of ether. The aqueous layer was acidified to pH ≤ 1 by addition of 3 N aqueous hydrochloric acid solution. The acidic aqueous solution was extracted with three 30-mL portions of ether. These combined organic extracts were washed sequentially with water (15 mL) and saturated aqueous sodium chloride solution (15 mL). The washed organic extracts were dried over sodium sulfate. The dried solution was filtered, and the filtrate was concentrated to afford acid **99** as a clear, colorless liquid (187 mg, 97%). Coupling of acid **99** (32.1 mg, 0.247 mmol, 1 equiv) with (*R*)-(α-methylbenzyl)amine (37.7 μL, 0.296 mmol, 1.20 equiv) in the presence of 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride (70.9 mg, 0.370 mmol, 1.50 equiv), 1-hydroxybenzotriazole hydrate (56.6 mg, 0.370 mmol, 1.50 equiv), and triethylamine (137 μL, 0.986 mmol, 4.00 equiv) in *N*,*N*-dimethyformamide (500 μL) at

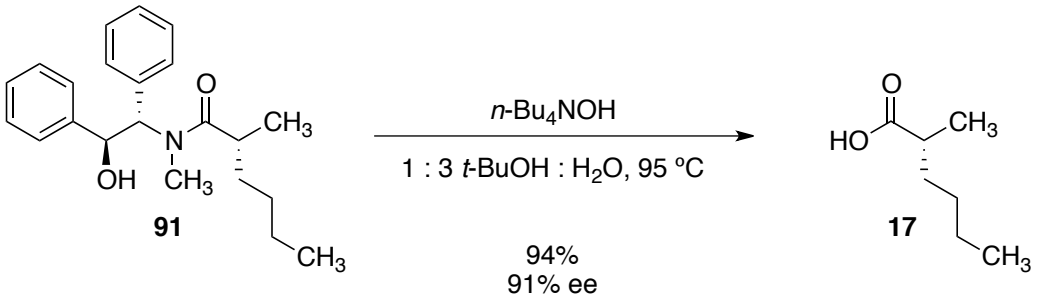
23 ºC for 20 h gave the corresponding (*R*)-(α-methylbenzyl)amide, which was analyzed by chiral capillary GC to establish an ee of 95% for acid **99** (Restek Rt-βDEXsm column, 30 m, 0.23 mmID, oven temperature 190 ºC, t_R(minor) = 5.59 min, t_R(major) = 5.93 min). The characterization data obtained for acid **99** were in agreement with values previously reported.[50]



(*R*)-2-methyl-3-phenylpropanoic acid (16)

An aqueous solution of tetra-*n*-butylammonium hydroxide (40% w/w, 4.39 mL, 6.69 mmol, 5.00 equiv) was added in one portion to a stirring biphasic mixture of amide **90** (500 mg, 1.34 mmol, 1 equiv) in *tert*-butyl alcohol (5 mL) and water (15 mL). The resulting biphasic mixture was stirred for 24 h at 95 ºC and then cooled to 23 ºC. The biphasic mixture was partitioned between 0.5 N aqueous sodium hydroxide solution (200 mL) and ether (30 mL). The layers were separated. The aqueous layer was extracted with two 30-mL portions of ether. The aqueous layer was acidified to pH ≤ 1 by the addition of 3 N aqueous hydrochloric acid solution. The resulting acidic aqueous solution was saturated with sodium chloride and then extracted with three 35-mL portions of ether. The combined organic extracts were washed with water (15 mL) and then dried over sodium sulfate. The dried solution was filtered, and the filtrate was concentrated to afford acid **16** as a clear liquid (219 mg, 99%). Coupling of acid **16** (25.0 mg, 0.152 mmol, 1 equiv) with (*R*)-(α-methylbenzyl)amine (23.0 μL, 0.183 mmol, 1.20 equiv) in the presence of 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride (43.8 mg, 0.228 mmol, 1.50 equiv), 1-hydroxybenzotriazole hydrate (30.9 mg, 0.228 mmol, 1.50 equiv), and triethylamine (85.0 μL, 0.609 mmol, 4.00 equiv) in *N*,*N*-dimethylformamide (500 μL) at 23 ºC for 20 h gave the corresponding (*R*)-(α-methylbenzyl)amide which was analyzed by chiral capillary GC to establish an ee of 95%

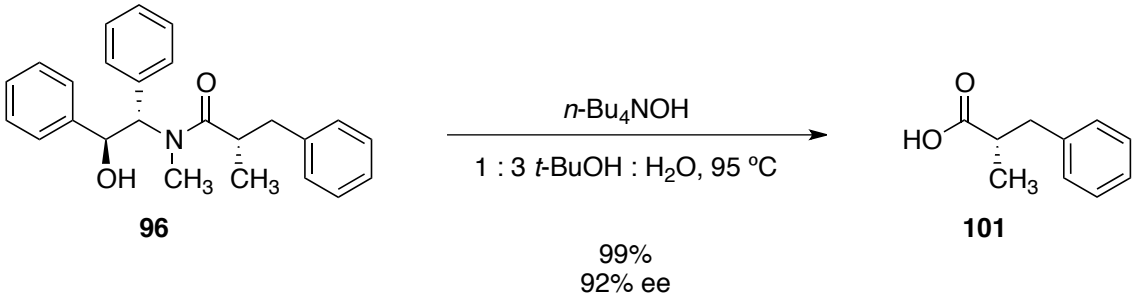
for acid **16** (Restek Rt-βDEXsm column, 30 m, 0.23 mmID, oven temperature 190 ºC, t_R (major, amide) = 22.0 min, t_R (minor, amide) = 24.8 min). The characterization data obtained for acid **16** were in agreement with values previously reported.[50]



(*R*)-2-methylhexanoic acid (17)

An aqueous solution of tetra-*n*-butylammonium hydroxide (40% w/w, 4.83 mL, 7.36 mmol, 5.00 equiv) was added in one portion to a stirring biphasic mixture of amide **91** (500 mg, 1.47 mmol, 1 equiv) in *tert*-butyl alcohol (5 mL) and water (15 mL). The resulting biphasic mixture was stirred for 24 h at 95 ºC and then cooled to 23 ºC. The biphasic mixture was partitioned between 0.5 N aqueous sodium hydroxide solution (200 mL) and ether (30 mL). The layers were separated. The aqueous layer was extracted with two 30-mL portions of ether. The aqueous layer was acidified to pH ≤ 1 by the addition of 3 N aqueous hydrochloric acid solution. The resulting acidic aqueous solution was saturated with sodium chloride and then extracted with three 40-mL portions of ether. The combined organic extracts were washed with water (15 mL) and then dried over sodium sulfate. The dried solution was filtered, and the filtrate was concentrated to afford acid **17** as a clear liquid (180 mg, 94%). Coupling of acid **17** (25.0 mg, 0.192 mmol, 1 equiv) with (*R*)-(α-methylbenzyl)amine (29.3 μL, 0.230 mmol, 1.20 equiv) in the presence of 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride (55.2 mg, 0.288 mmol, 1.50 equiv), 1-hydroxybenzotriazole hydrate (38.9 mg, 0.288 mmol, 1.50 equiv), and triethylamine (107 μL, 0.768 mmol, 4.00 equiv) in *N*,*N*-dimethylformamide (640 μL) at 23 ºC for 20 h gave the corresponding (*R*)-(α-methylbenzyl)amide which was analyzed by chiral capillary GC to establish an ee of 91%

for acid **17** (Restek Rt-βDEXsm column, 30 m, 0.23 mmID, oven temperature 190 ºC, t_R (minor, amide) = 5.6 min, t_R (major, amide) = 5.9 min). The characterization data obtained for acid **17** were in agreement with values previously reported.[50]

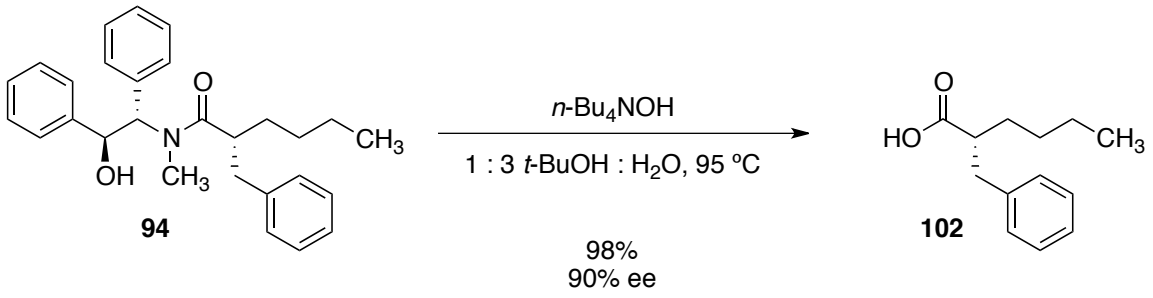


96 **101**

(*S*)-2-methyl-3-phenylpropanoic acid (101)

An aqueous solution of tetra-*n*-butylammonium hydroxide (40% w/w, 4.50 mL, 6.86 mmol, 5.00 equiv) was added in one portion to a stirring biphasic solution of amide **96** (512 mg, 1.37 mmol, 1 equiv) and in *tert*-butyl alcohol (5.17 mL) and water (15.5 mL). The resulting biphasic mixture was stirred for 24 h at 95 ºC and then cooled to 23 ºC. The mixture was partitioned between 0.5 N aqueous sodium hydroxide solution (200 mL) and ether (30 mL). The layers were separated. The aqueous layer was extracted with two 30-mL portions of ether. The aqueous layer was acidified to pH ≤ 1 by addition of 3 N aqueous hydrochloric acid solution. The acidic aqueous solution was extracted with three 30-mL portions of ether. These combined organic extracts were washed sequentially with water (15 mL) and saturated aqueous sodium chloride solution (15 mL). The washed organic extracts were dried over sodium sulfate. The dried solution was filtered, and the filtrate was concentrated to afford acid **101** as a clear, colorless liquid (224 mg, 99%). Coupling of acid **101** (31.3 mg, 0.191 mmol, 1 equiv) with (*R*)-(α-methylbenzyl)amine (29.1 μL, 0.229 mmol, 1.20 equiv) in the presence of 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride (54.8 mg, 0.286 mmol, 1.50 equiv), 1-hydroxybenzotriazole hydrate (43.8 mg, 0.286 mmol, 1.50 equiv), and triethylamine (106 μL, 0.762 mmol, 4.00 equiv) in *N*,*N*-dimethyformamide (500 μL) at 23 ºC for 20 h gave the corresponding (*R*)-(α-methylbenzyl)amide, which was analyzed by chiral capillary

GC to establish an ee of 92% for acid **101** (Restek Rt-βDEXsm column, 30 m, 0.23 mmID, oven temperature 190 ºC, t_R(minor) = 22.0 min, t_R(major) = 24.9 min). The characterization data obtained for acid **101** were in agreement with values previously reported.[50]

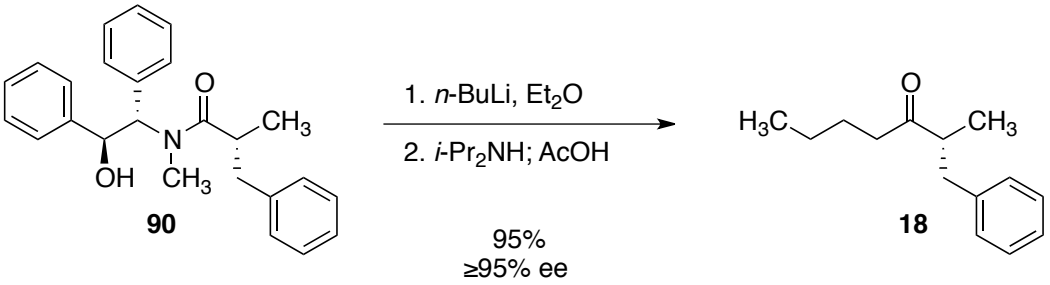


(*R*)-2-benzylhexanoic acid (102)

An aqueous solution of tetra-*n*-butylammonium hydroxide (40% w/w, 3.95 mL, 6.03 mmol, 5.00 equiv) was added in one portion to a stirring biphasic solution of amide **94** (501 mg, 1.21 mmol, 1 equiv) and in *tert*-butyl alcohol (4.5 mL) and water (13.5 mL). The resulting biphasic mixture was stirred for 20 h at 95 ºC and then cooled to 23 ºC. The mixture was partitioned between 0.5 N aqueous sodium hydroxide solution (200 mL) and ether (30 mL). The layers were separated. The aqueous layer was extracted with two 30-mL portions of ether. The aqueous layer was acidified to pH ≤ 1 by addition of 3 N aqueous hydrochloric acid solution. The acidic aqueous solution was extracted with three 30-mL portions of ether. These combined organic extracts were washed sequentially with water (15 mL) and saturated aqueous sodium chloride solution (15 mL). The washed organic extracts were dried over sodium sulfate. The dried solution was filtered, and the filtrate was concentrated to afford acid **102** as a clear, colorless liquid (245 mg, 98%). Coupling of acid **102** (26.2 mg, 0.127 mmol, 1 equiv) with (*R*)-(α-methylbenzyl)amine (19.4 μL, 0.152 mmol, 1.20 equiv) in the presence of 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride (36.5 mg, 0.191 mmol, 1.50 equiv), 1-hydroxybenzotriazole hydrate (29.2 mg, 0.191 mmol, 1.50 equiv), and triethylamine (70.8 μL, 0.508 mmol, 4.00 equiv) in *N*,*N*-dimethyformamide (500 μL) at 23 ºC for 20 h gave the corresponding (*R*)-(α-methylbenzyl)amide, which was analyzed by chiral

capillary GC to establish an ee of 90% for acid **102** (Restek Rt-βDEXsm column, 30 m, 0.23 mmID, oven temperature 190 ºC, t_R(major) = 45.9 min, t_R(minor) = 47.8 min). The characterization data obtained for acid **102** were in agreement with values previously reported.[50]

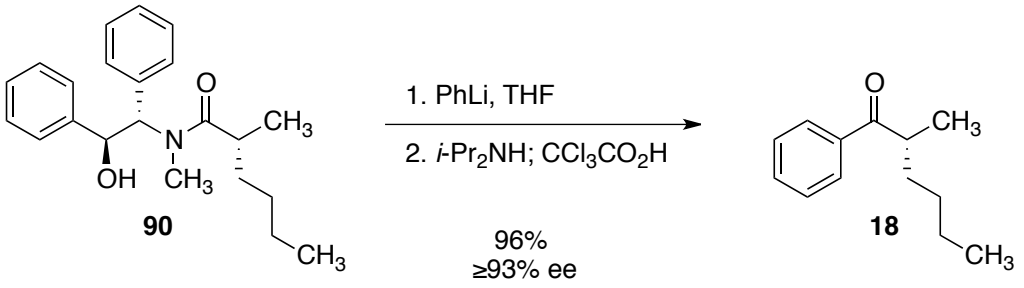
Addition of organolithium reagents to form ketones:



(*R*)-2-methyl-1-phenylheptan-3-one (18)

Amide **90** (500 mg, 1.34 mmol, 1 equiv) was suspended in toluene (10 mL). The suspension was warmed to 70 ºC to dissolve the amide, and the resulting solution was concentrated under reduced pressure. The reaction flask was flushed with dry argon, ether (10.5 mL) was added, and the resulting suspension was cooled to –78 ºC. A freshly titrated solution of *n*-butyllithium in hexanes (2.40 M, 1.34 mL, 2.40 equiv) was added by syringe, and the mixture was warmed to 0 ºC and held at that temperature for 20 min. Excess *n*-butyllithium was quenched at 0 ºC by the addition of *N*,*N*-diisopropylamine (0.188 mL, 1.34 mmol, 1 equiv). After 15 min, a solution of acetic acid in ether (20% v/v, 10 mL) was added. The mixture was partitioned between ethyl acetate (20 mL) and water (20 mL). The layers were separated. The aqueous layer was extracted with two 20-mL portions of dichloromethane. The combined organic extracts were dried over sodium sulfate. The dried solution was filtered, and the filtrate was concentrated. The residue was purified by flash column chromatography (2→5% ethyl acetate–hexanes) to afford ketone **18** as a clear, colorless liquid (261 mg, 95%). Solid lithium aluminum hydride (13.9 mg, 0.367 mmol, 1.50 equiv) was added to a solution of ketone **18** (50.0 mg, 0.245 mmol, 1 equiv) in ether (490 μL) at 0 ºC for 25 min to afford a mixture of diastereomeric alcohols. Acylation of the mixture of diastereomeric alcohols (7.50 mg, 0.036 mmol, 1

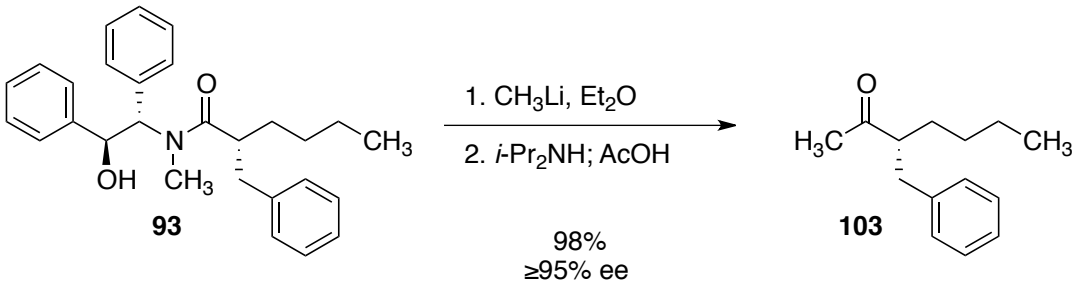
equiv) with (*R*)- or (S)-Mosher acid chloride (20.4 μL, 0.109 mmol, 3.00 equiv) in the presence of 4-(dimethylamino)-pyridine (22.2 mg, 0.182 mmol, 5.00 equiv) and triethylamine (25.3 μL, 0.182 mmol, 5.00 equiv) in dichloromethane (1 mL) at 23 ºC for 20 min, followed by ^{1}H-NMR analysis of the corresponding Mosher ester derivatives, established that ketone **18** was of ≥95% ee. The characterization data obtained for ketone **18** were in agreement with values previously reported.[50]



(*R*)-2-methyl-1-phenylhexan-1-one (19)

Amide **91** (200 mg, 0.589 mmol, 1 equiv) was dissolved in toluene (5 mL). The solution was warmed to 70 ºC and then was concentrated under reduced pressure. The reaction flask was flushed with dry argon, tetrahydrofuran (10 mL) was added, and the resulting solution was cooled to –78 ºC. A freshly titrated solution of phenyllithium in di-*n*-buytl ether (1.80 M, 0.982 mL, 3.00 equiv) was added by syringe, and the mixture was stirred for 20 min at 0 ºC and for 10 min at 23 ºC. Excess phenyllithium was quenched at 0 ºC by the addition of *N*,*N*-diisopropylamine (83.0 μL, 0.589 mmol, 1.00 equiv). After 15 min, a solution of trichloroacetic acid in ether (10% v/v, 10 mL) was added. The mixture was partitioned between ethyl acetate (40 mL) and saturated aqueous sodium bicarbonate solution (50 mL). The layers were separated. The organic layer was washed sequentially with saturated aqueous sodium bicarbonate solution (50 mL) and water (50 mL). The washed organic extract was dried over sodium sulfate. The dried solution was filtered, and the filtrate was concentrated. The residue was purified by flash column chromatography (0→5% ethyl acetate–hexanes) to afford ketone **19** as a pale-yellow liquid (109 mg, 96%). Solid lithium aluminum hydride (12.0 mg, 0.315 mmol, 1.50 equiv) was added to a solution of ketone **19** (40.0 mg, 0.210 mmol, 1 equiv) in ether (500 μL) at 0 ºC for 25 min to afford a mixture of diastereomeric alcohols. Acylation of the mixture of diastereomeric alcohols (10.0 mg, 0.052 mmol, 1 equiv) with (*R*)- or (S)-

Mosher acid chloride (29.1 μL, 0.156 mmol, 3.00 equiv) in the presence of 4-(dimethylamino)-pyridine (31.8 mg, 0.260 mmol, 5.00 equiv) and triethylamine (36.2 μL, 0.260 mmol, 5.00 equiv) in dichloromethane (1 mL) at 23 ºC for 20 min, followed by ^{1}H-NMR analysis of the corresponding Mosher ester derivatives, established that ketone **19** was of ≥93% ee. The characterization data obtained for ketone **19** were in agreement with values previously reported.[50]

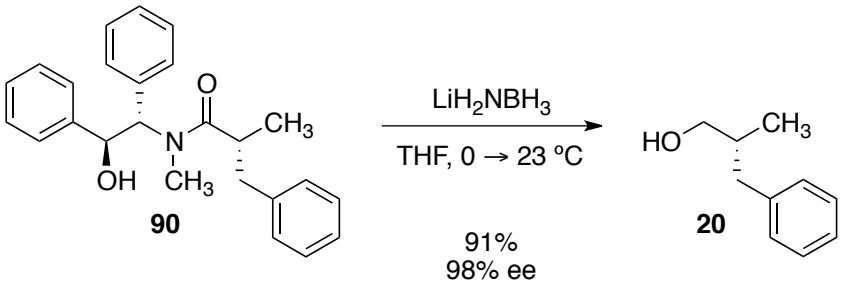


(*R*)-3-benzylheptan-2-one (103)

Amide **94** (203 mg, 0.489 mmol, 1 equiv) was suspended in toluene (4 mL). The suspension was warmed to 70 ºC to dissolve the amide, and the resulting solution was concentrated under reduced pressure. The reaction flask was flushed with dry argon, ether (5.0 mL) was added, and the resulting suspension was cooled to –78 ºC. A freshly titrated solution of methyllithium in diethoxymethane (2.85 M, 515 µL, 3.00 equiv) was added by syringe, and the mixture was stirred for 30 min to 0 ºC and for 10 min at 23 ºC. Excess methyllithium was quenched at 0 ºC by the addition of *N*,*N*-diisopropylamine (68.6 µL, 0.489 mmol, 1 equiv). After 15 min, a solution of acetic acid in ether (10% v/v, 10 mL) was added. The mixture was partitioned between ethyl acetate (40 mL) and saturated aqueous sodium bicarbonate solution (50 mL). The layers were separated. The organic layer was washed sequentially with saturated aqueous sodium bicarbonate solution (25 mL), water (25 mL), and saturated aqueous sodium chloride solution (25 mL). The washed organic layer was dried over sodium sulfate. The dried solution was filtered, and the filtrate was concentrated. The residue was purified by flash column chromatography (1→5% ethyl acetate–hexanes) to afford ketone **103** as a clear, colorless liquid (97.5 mg, 98%). Solid lithium aluminum hydride (13.4 mg, 0.325 mmol, 1.50 equiv) was added to a solution of ketone **103** (48.0 mg, 0.235 mmol, 1 equiv) in ether (940 µL) at 0 ºC for 30 min to afford a mixture of diastereomeric alcohols. Acylation of

the mixture of diastereomeric alcohols (10.0 mg, 0.048 mmol, 1 equiv) with (*R*)- or (S)-Mosher acid chloride (36.7 μL, 0.145 mmol, 3.00 equiv) in the presence of 4-(dimethylamino)-pyridine (29.6 mg, 0.242 mmol, 5.00 equiv) and triethylamine (34.0 μL, 0.242 mmol, 5.00 equiv) in dichloromethane (1.5 mL) at 23 ºC for 10 h, followed by ^{1}H-NMR analysis of the corresponding Mosher ester derivatives, established that ketone **103** was of ≥95% ee. The characterization data obtained for ketone **103** were in agreement with values previously reported.[50]

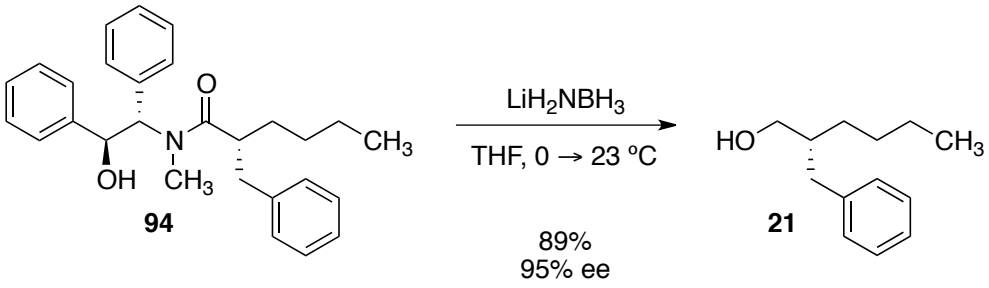
Reduction with lithium amidotrihydroborate to form primary alcohols:



(*R*)-2-methyl-3-phenylpropan-1-ol (20)

A freshly titrated solution of *n*-butyllithium in hexanes (2.40 M, 2.18 mL, 3.90 equiv) was added by syringe to a stirring solution of *N*,*N*-diisopropylamine (0.79 mL, 5.62 mmol, 4.20 equiv) in tetrahydrofuran (5.6 mL) at –78 ºC. The resulting solution was stirred at –78 ºC for 10 min, then was warmed to 0 ºC and held at that temperature for 10 min. Borane-ammonia complex (90%, 184 mg, 5.35 mmol, 4.00 equiv) was added in one portion, and the suspension was stirred at 0 ºC for 15 min and then was warmed to 23 ºC. After 15 min, the solution was cooled to 0 ºC. A solution of amide **90** (500 mg, 1.34 mmol, 1 equiv) in tetrahydrofuran (3.4 mL, followed by a 0.6-mL rinse) was added via cannula. The reaction mixture was allowed to warm to 23 ºC. After 1 h, the reaction mixture was cooled in an ice-bath and 3 N aqueous hydrochloric acid solution (15 mL) was added carefully (Caution: evolution of dihydrogen). After stirring for 30 min at 0 ºC the product solution was extracted with four 20-mL portions of ether. The combined organic extracts were washed sequentially with 3 N aqueous hydrochloric acid solution (15 mL), 2 N aqueous sodium hydroxide solution (15 mL), and saturated aqueous sodium chloride solution (15 mL). The washed organic extracts were dried over magnesium sulfate. The dried solution was filtered, and the filtrate was concentrated. The residue was purified by flash column chromatography (40 → 60% ether-pentane) to afford

alcohol **20** as a clear liquid (183 mg, 91%). Chiral HPLC analysis (Chiralcel OD-H, 95:5 hexanes:*i*-PrOH, 1 mL/min, λ = 220 nm, t_R (minor, alcohol **104**) = 8.23 min, t_R (major, alcohol **20**) = 9.57 min) of alcohol **20** established that alcohol **20** was of 98% ee. The characterization data obtained for alcohol **20** were in agreement with values previously reported.[50]

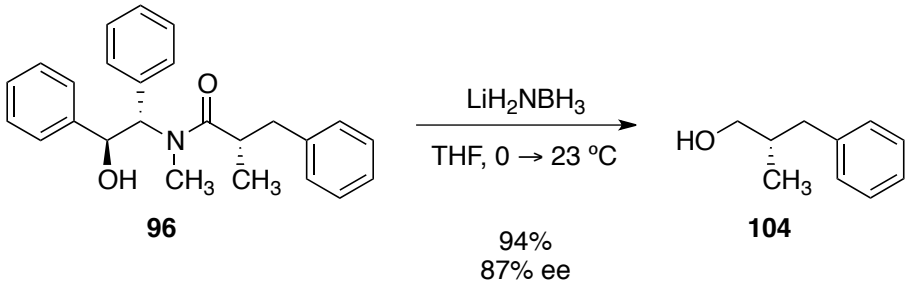


(*R*)-2-benzylhexan-1-ol (21)

A freshly titrated solution of *n*-butyllithium in hexanes (2.46 M, 767 μL, 3.90 equiv) was added by syringe to a stirring solution of *N*,*N*-diisopropylamine (290 μL, 2.03 mmol, 4.20 equiv) in tetrahydrofuran (1.4 mL) at –78 ºC. The resulting solution was stirred at –78 ºC for 10 min, then was warmed to 0 ºC and held at that temperature for 10 min. Borane–ammonia complex (90%, 66.4 mg, 1.93 mmol, 4.00 equiv) was added in one portion, and the suspension was stirred at 0 ºC for 15 min and then was warmed to 23 ºC. After 15 min, the solution was cooled to 0 ºC. A solution of amide **94** (201 mg, 0.484 mmol, 1 equiv) in tetrahydrofuran (1.0 mL, followed by a 1.0 mL rinse) was added via cannula. The reaction mixture was allowed to warm to 23 ºC. After 1.5 h, the reaction mixture was cooled in an ice-bath and 3 N aqueous hydrochloric acid solution (6 mL) was added carefully (Caution: evolution of dihydrogen). After stirring for 30 min at 0 ºC, the product solution was extracted with four 10-mL portions of ether. The combined organic extracts were washed sequentially with 3 N aqueous hydrochloric acid solution (10 mL), 2 N aqueous sodium hydroxide solution (6 mL), and saturated aqueous sodium chloride solution (6 mL). The washed organic extracts were dried over magnesium sulfate. The dried solution was filtered, and the filtrate was concentrated. The residue was purified by flash column chromatography on silica gel pre-treated with 20% triethylamine–hexanes (20% ethyl acetate–hexanes) to afford alcohol **21** as a clear, colorless liquid (82.5 mg,

89%). Chiral HPLC analysis (Chiralcel OD-H, 95:5 hexanes:*i*-PrOH, 1 mL/min, λ = 220 nm, t_R (minor)[51] = 6.68 min, t_R (major, alcohol **21**) = 8.12 min) of alcohol **21** established that alcohol **21** was of 95% ee. The characterization data obtained for alcohol **21** were in agreement with values previously reported.[50]

[51] An authentic sample of the enantiomer of alcohol **21** was prepared for this analysis.



96 **104**

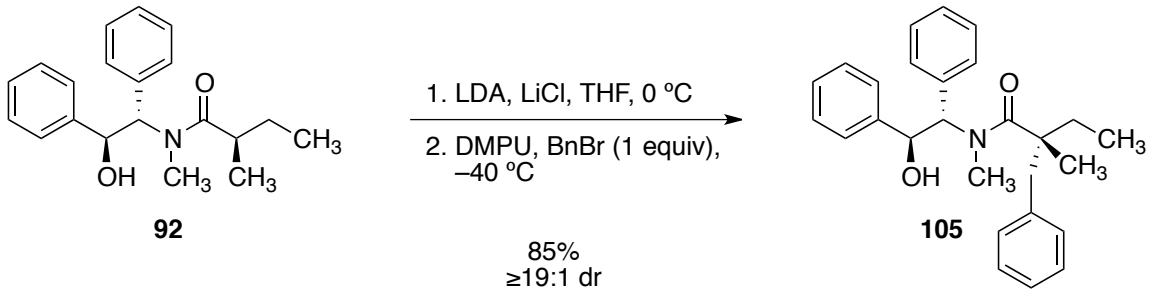
94%
87% ee

(*S*)-2-methyl-3-phenylpropan-1-ol (104)

A freshly titrated solution of *n*-butyllithium in hexanes (2.45 M, 2.21 mL, 3.90 equiv) was added by syringe to a stirring solution of *N*,*N*-diisopropylamine (830 μL, 5.83 mmol, 4.20 equiv) in tetrahydrofuran (5.0 mL) at –78 ºC. The resulting solution was stirred at –78 ºC for 10 min, then was warmed to 0 ºC and held at that temperature for 10 min. Borane–ammonia complex (90%, 190 mg, 5.55 mmol, 4.00 equiv) was added in one portion, and the suspension was stirred at 0 ºC for 15 min and then was warmed to 23 ºC. After 15 min, the solution was cooled to 0 ºC. A solution of amide **96** (518 mg, 1.39 mmol, 1 equiv) in tetrahydrofuran (4.0 mL, followed by a 0.91 mL rinse) was added via cannula. The reaction mixture was allowed to warm to 23 ºC. After 1 h, the reaction mixture was cooled in an ice-bath and 3 N aqueous hydrochloric acid solution (15 mL) was added carefully (Caution: evolution of dihydrogen). After stirring for 30 min at 0 ºC, the product solution was extracted with four 20-mL portions of ether. The combined organic extracts were washed sequentially with 3 N aqueous hydrochloric acid solution (15.0 mL), 2 N aqueous sodium hydroxide solution (15 mL), and saturated aqueous sodium chloride solution (15 mL). The organic solution was dried over magnesium sulfate. The dried solution was filtered, and the filtrate was concentrated. The residue was purified by flash column chromatography on silica gel pre-treated with 20% triethylamine–hexanes (25% ethyl acetate–hexanes) to afford alcohol **104** as a clear,

colorless liquid (195 mg, 94%). Chiral HPLC analysis (Chiralcel OD-H, 95:5 hexanes:*i*-PrOH, 1 mL/min, λ = 220 nm, t_R (major, alcohol **104**) = 8.40 min, t_R (minor, alcohol **20**) = 9.97 min) of alcohol **104** established that alcohol **104** was of 87% ee. The characterization data obtained for alcohol **104** were in agreement with values previously reported.[50]

Enolization–alkylation of α,α-disubstituted pseudoephenamine amides depicted in Table 3.2:



(*R*)-2-benzyl-*N*-[(1*S*,2*S*)-2-hydroxy-1,2-diphenylethyl]-*N*,2-dimethylbutanamide (105)

N,*N*-Diisopropylamine (113 μL, 0.952 mmol, 2.28 equiv) was added by syringe to a stirring suspension of lithium chloride (124 mg, 2.92 mmol, 7.00 equiv) in tetrahydrofuran (700 μL) at 23 ºC. The resulting slurry was cooled to –78 ºC. A freshly titrated solution of *n*-butyllithium in hexanes (2.38 M, 400 μL, 2.28 equiv) was added by syringe. The reaction mixture was warmed briefly to 0 ºC (5 min), then was cooled to –78 ºC. An ice-cooled solution of amide **92** (156 mg, 0.501 mmol, 1.20 equiv) in tetrahydrofuran (600 μL) was then added by syringe. The transfer was quantitated with tetrahydrofuran (400 μL). The reaction mixture was stirred for 3 h at 0 ºC. The yellow heterogeneous mixture was cooled to –40 ºC, then DMPU (164 μL, 1.35 mmol, 3.25 equiv) was added by syringe and stirring was continued for 15 min at –40 ºC, whereupon benzyl bromide (50.0 μL, 0.417 mmol, 1 equiv) was added by syringe. The mixture was stirred for 1.25 h at –40 ºC, then saturated aqueous ammonium chloride solution (1.5 mL) was added and the biphasic mixture was warmed to 23 ºC. The biphasic mixture was partitioned between ethyl acetate (20 mL) and a 1:1 mixture of saturated aqueous sodium chloride solution and 1 N aqueous hydrochloric acid solution (30 mL). The layers were

separated. The aqueous layer was extracted with two 20-mL portions of ethyl acetate. The combined organic extracts were dried over sodium sulfate. The dried solution was filtered, and the filtrate was concentrated. The residue was purified by flash column chromatography (10→50% ethyl acetate–hexanes) to provide amide **105** as an off-white solid (143 mg, 85%). The diastereomeric ratio of the purified product was determined to be ≥19:1 by ^{1}H NMR analysis of the corresponding cyclic oxazolinium triflate derivative (see below). TLC (40% Ethyl acetate–hexanes): R_f = 0.69 (UV, $KMnO_4$). ^{1}H NMR (500 MHz, $CDCl_3$), δ: 7.46-7.08 (m, 15H), 5.85 (d, 1H, *J* = 9.0 Hz), 5.33 (dd, 1H, *J* = 9.5, 7.0 Hz), 3.69 (d, 1H, *J* = 6.0 Hz), 3.12 (d, 1H, *J* = 14.0 Hz), 2.94 (s, 3H), 2.81 (d, 1H, *J* = 13.5 Hz), 1.93 (dq, 1H, *J* = 14.5, 7.5 Hz), 1.42 (dq, 1H, *J* = 15.0, 7.5 Hz), 1.20 (s, 3H), 0.81 (t, 3H, *J* = 7.7 Hz). ^{13}C NMR (125 MHz, $CDCl_3$), δ: 178.5, 141.9, 137.9, 136.8, 130.5, 129.1, 128.4, 128.2, 128.0, 127.7, 127.6, 127.1, 126.4, 73.3, 66.3, 48.8, 45.3, 33.7, 32.2, 23.6, 9.0. FTIR (neat), cm^{-1}: 3404 (br), 2970, 1601 (s), 1452, 1080, 908. HRMS (ESI): Calcd for $(C_{27}H_{31}NO_2 + H)^+$: 402.2428. Found: 402.2423.

Assignment of absolute stereochemistry of α-quaternary alkylation product established by X-ray crystallographic analysis:

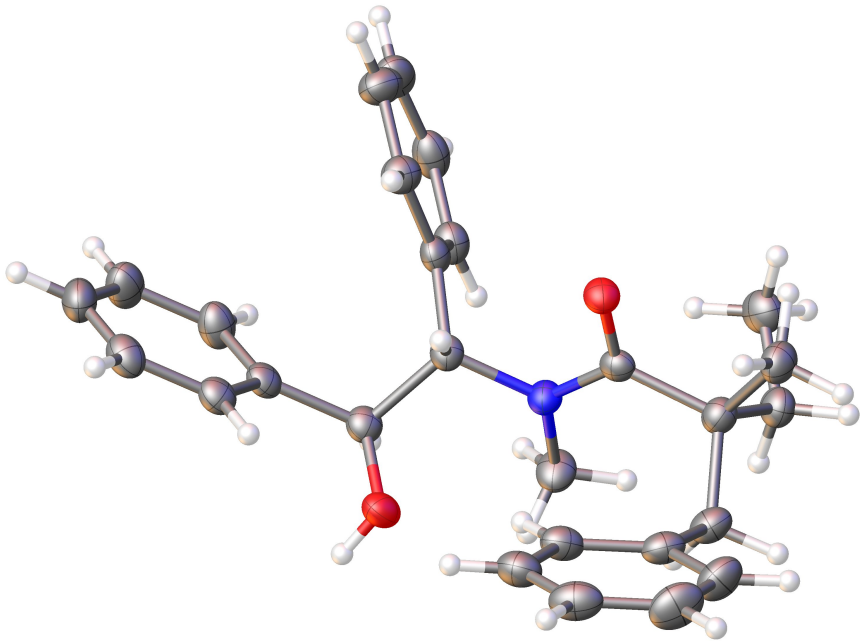
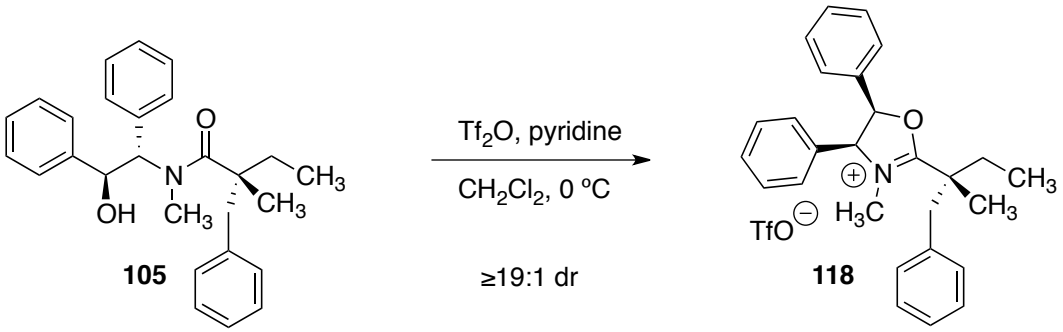
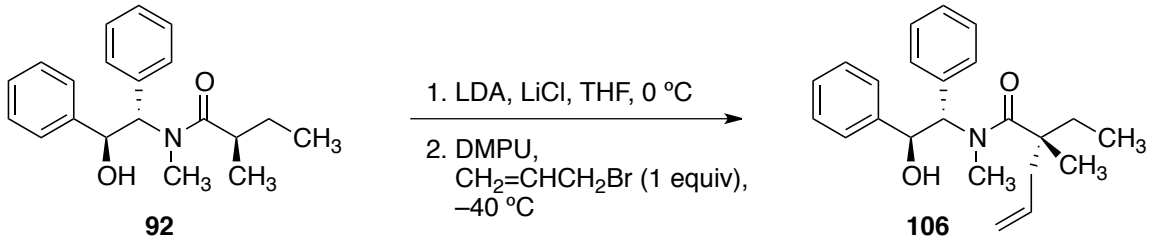


Figure 3.9 X-ray crystal structure of pseudoephenamine amide **105**.



Cyclic oxazolinium triflate (118)

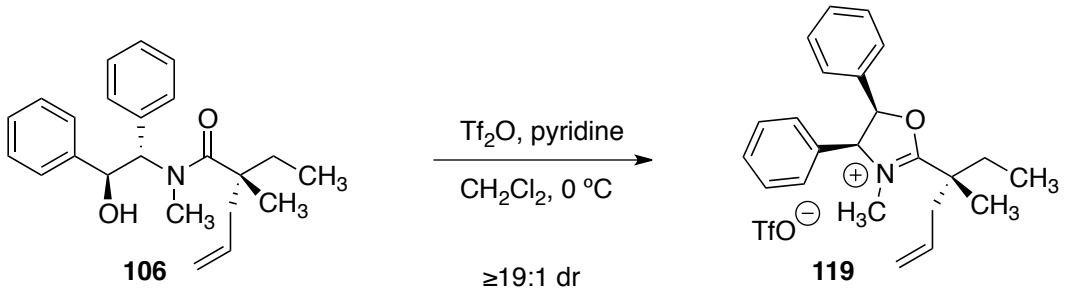
Trifluoromethanesulfonic anhydride (17.0 μL, 0.100 mmol, 2.00 equiv) was added dropwise by syringe to a stirring solution of the α-quaternary amide **105** (20.0 mg, 0.050 mmol, 1 equiv) and pyridine (12.0 μL, 0.149 mmol, 3.00 equiv) in dichloromethane (2 mL) at 0 °C. The reaction mixture was stirred for 10 min at 0 °C. The product solution was concentrated by rotary evaporation at ~40 mmHg, then with a vacuum manifold at 0.1 mmHg for 3 h. The diastereomeric ratio of the residue was determined to be ≥19:1 by ^{1}H NMR analysis. ^{1}H NMR (≥19:1 diastereomeric ratio, asterisk denotes pyridinium ion peaks, 500 MHz, $CDCl_3$), δ: 8.88* (d, 1H, *J* = 4.9 Hz), 8.47* (t, 1H, *J* = 7.8 Hz), 7.99* (t, 1H, *J* = 7.1 Hz), 7.54-7.03 (m, 14H), 6.87-6.80 (m, 2H), 6.41 (d, 1H, *J* = 11.5 Hz), 3.36 (s, 3H), 3.29 (d, 1H, *J* = 14.5 Hz), 3.22 (d, 1H, *J* = 14.0 Hz), 2.30 (dq, 1H, *J* = 14.5, 7.5 Hz), 1.83 (dq, 1H, *J* = 15.0, 7.5 Hz), 1.67 (s, 3H), 1.24 (t, 3H, *J* = 7.7 Hz).



(*R*)-2-ethyl-*N*-[(1*S*,2*S*)-2-hydroxy-1,2-diphenylethyl]-*N*,2-dimethylpent-4-enamide (106)

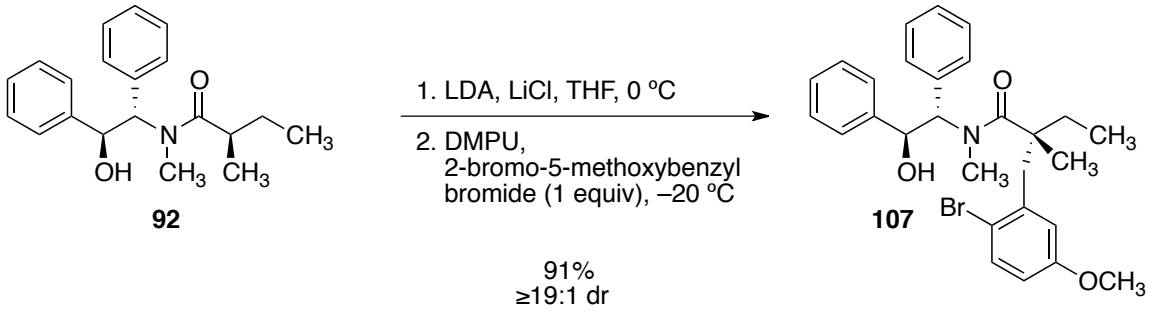
N,*N*-Diisopropylamine (131 μL, 0.938 mmol, 2.92 equiv) was added by syringe to a stirring suspension of lithium chloride (123 mg, 2.89 mmol, 9.00 equiv) in tetrahydrofuran (600 μL) at 23 ºC. The resulting slurry was cooled to –78 ºC. A freshly titrated solution of *n*-butyllithium in hexanes (2.38 M, 394 μL, 2.92 equiv) was added by syringe. The reaction mixture was warmed briefly to 0 ºC (5 min), then was cooled to –78 ºC. An ice-cooled solution of amide **92** (150 mg, 0.482 mmol, 1.50 equiv) in tetrahydrofuran (600 μL) was then added by syringe. The transfer was quantitated with tetrahydrofuran (400 μL). The reaction mixture was stirred for 3 h at 0 ºC. The yellow heterogeneous mixture was cooled to –40 ºC, then DMPU (146 μL, 1.21 mmol, 3.76 equiv) was added by syringe and stirring was continued for 15 min at –40 ºC, whereupon allyl bromide (28.0 μL, 0.321 mmol, 1 equiv) was added by syringe. The mixture was stirred for 5 h at –40 ºC, then saturated aqueous ammonium chloride solution (1.5 mL) was added and the biphasic mixture was warmed to 23 ºC. The biphasic mixture was partitioned between ethyl acetate (20 mL) and a 1:1 mixture of saturated aqueous sodium chloride solution and 1 N aqueous hydrochloric acid solution (30 mL). The layers were separated. The aqueous layer was extracted with two 20-mL portions of ethyl acetate.

The combined organic extracts were dried over sodium sulfate. The dried solution was filtered, and the filtrate was concentrated. The residue was purified by flash column chromatography (10→50% ethyl acetate–hexanes) to provide amide **106** as a white solid (113 mg, 99%). The diastereomeric ratio of the purified product was determined to be ≥19:1 by ^{1}H NMR analysis of the corresponding cyclic oxazolinium triflate derivative (see below). TLC (40% Ethyl acetate–hexanes): R_f = 0.69 (UV, $KMnO_4$). ^{1}H NMR (500 MHz, $CDCl_3$), δ: 7.45-7.16 (m, 10H), 5.87 (d, 1H, *J* = 9.5 Hz), 5.85-5.75 (m, 1H), 5.32 (dd, 1H, *J* = 9.0, 7.0 Hz), 5.13-5.05 (m, 2H), 3.77 (d, 1H, *J* = 5.5 Hz), 2.97 (s, 3H), 2.59 (dd, 1H, *J* = 14.0, 6.5 Hz), 2.23 (dd, 1H, *J* = 14.0, 7.5 Hz), 1.77 (dq, 1H, *J* = 14.5, 7.5 Hz), 1.52 (dq, 1H, *J* = 15.0, 7.5 Hz), 1.23 (s, 3H), 0.80 (t, 3H, *J* = 7.5 Hz). ^{13}C NMR (125 MHz, $CDCl_3$), δ: 178.2, 141.8, 136.9, 134.7, 128.9, 128.3, 128.2, 127.6, 127.5, 127.1, 117.7, 73.0, 66.0, 47.4, 43.7, 33.5, 31.6, 23.9, 8.9. FTIR (neat), cm^{-1}: 3406 (br), 2974, 1601 (s), 1452, 1080, 912. HRMS (ESI): Calcd for $(C_{23}H_{29}NO_2 + H)^+$: 352.2271. Found: 352.2263.



Cyclic oxazolinium triflate (119)

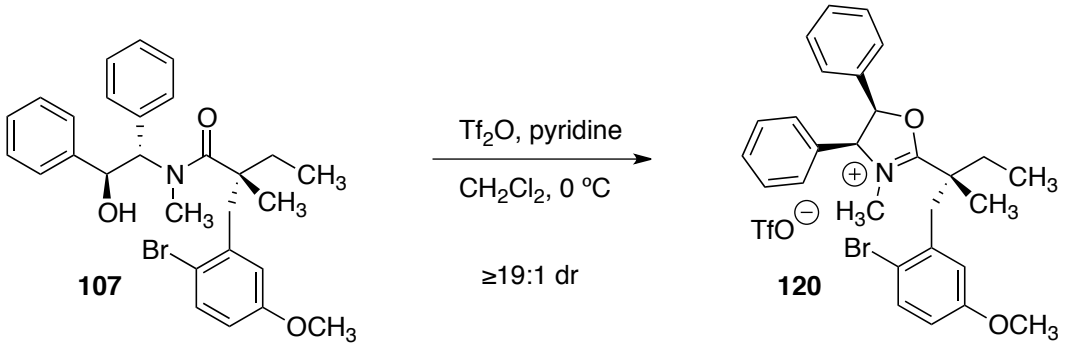
Trifluoromethanesulfonic anhydride (19.0 μL, 0.114 mmol, 2.00 equiv) was added dropwise by syringe to a stirring solution of the α-quaternary amide **106** (20.0 mg, 0.057 mmol, 1 equiv) and pyridine (14.0 μL, 0.171 mmol, 3.00 equiv) in dichloromethane (2 mL) at 0 °C. The reaction mixture was stirred for 10 min at 0 °C. The product solution was concentrated by rotary evaporation at ~40 mmHg, then with a vacuum manifold at 0.1 mmHg for 3 h. The diastereomeric ratio of the residue was determined to be ≥19:1 by ^{1}H NMR analysis. ^{1}H NMR (≥19:1 diastereomeric ratio, asterisk denotes pyridinium ion peaks, 500 MHz, $CDCl_3$), δ: 8.92* (t, 1H, *J* = 5.9 Hz), 8.57* (t, 1H, *J* = 8.1 Hz), 8.08* (t, 1H, *J* = 6.6 Hz), 7.24-7.12 (m, 6H), 6.98-6.91 (m, 4H), 6.89 (d, 1H, *J* = 11.0 Hz), 6.34 (d, 1H, *J* = 10.5 Hz), 5.99-5.88 (m, 1H), 5.44-5.27 (m, 2H), 3.50 (s, 3H), 2.79 (dd, 1H, *J* = 14.5, 7.5 Hz), 2.63 (dd, 1H, *J* = 14.0, 6.5 Hz), 2.17 (dq, 1H, *J* = 14.5, 7.5 Hz), 1.91 (dq, 1H, *J* = 15.5, 8.0 Hz), 1.64 (s, 3H), 1.19 (t, 3H, *J* = 7.5 Hz).



(*R*)-2-(2-bromo-5-methoxybenzyl)-*N*-[(1*S*,2*S*)-2-hydroxy-1,2-diphenylethyl]-*N*,2-dimethylbutanamide (107)

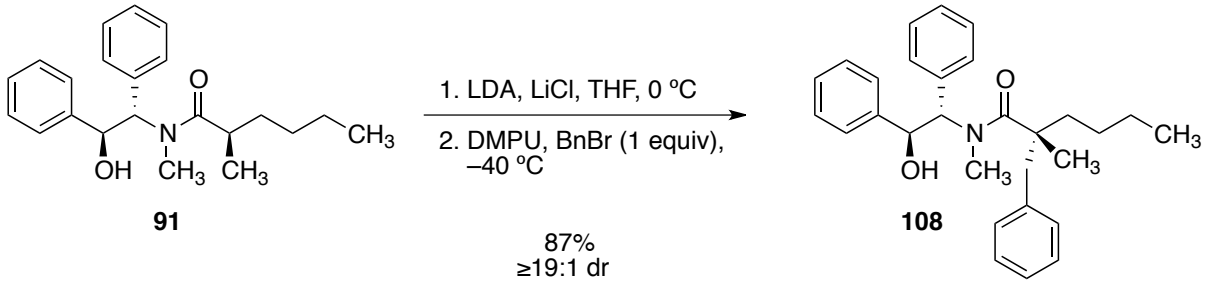
N,*N*-Diisopropylamine (176 μL, 1.25 mmol, 2.93 equiv) was added by syringe to a stirring suspension of lithium chloride (163 mg, 3.85 mmol, 9.00 equiv) in tetrahydrofuran (700 μL) at 23 ºC. The resulting slurry was cooled to –78 ºC. A freshly titrated solution of *n*-butyllithium in hexanes (2.38 M, 527 μL, 2.93 equiv) was added by syringe. The reaction mixture was warmed briefly to 0 ºC (5 min), then was cooled to –78 ºC. An ice-cooled solution of amide **92** (200 mg, 0.642 mmol, 1.50 equiv) in tetrahydrofuran (600 μL) was then added by syringe. The transfer was quantitated with tetrahydrofuran (400 μL). The reaction mixture was stirred for 3 h at 0 ºC. The yellow heterogeneous mixture was cooled to –20 ºC, then DMPU (194 μL, 1.60 mmol, 3.74 equiv) was added by syringe and stirring was continued for 15 min at –20 ºC, whereupon 2-bromo-5-methoxybenzyl bromide (120 mg, 0.428 mmol, 1 equiv) in THF (500 μL) was added by syringe. The mixture was stirred for 2 h at –20 ºC, then saturated aqueous ammonium chloride solution (1.5 mL) was added and the biphasic mixture was warmed to 23 ºC. The biphasic mixture was partitioned between ethyl acetate (20 mL) and a 1:1 mixture of saturated aqueous sodium chloride solution and 1 N aqueous hydrochloric acid solution (30 mL). The layers were separated. The aqueous layer was extracted with two 20-mL portions of ethyl acetate. The combined organic extracts were dried over sodium

sulfate. The dried solution was filtered, and the filtrate was concentrated. The residue was purified by flash column chromatography (10→40% ethyl acetate–hexanes) to provide amide **107** as a white foam/solid (198 mg, 91%). The diastereomeric ratio of the purified product was determined to be ≥19:1 by ^{1}H NMR analysis of the corresponding cyclic oxazolinium triflate derivative (see below).TLC (40% Ethyl acetate–hexanes): R_f = 0.59 (UV, $KMnO_4$). ^{1}H NMR (500 MHz, $CDCl_3$), δ: 7.42-7.41 (m, 1H), 7.30-7.17 (m, 10H), 6.96 (d, 1H, *J* = 3.0 Hz), 6.64 (dd, 1H, *J* = 9.0, 3.0 Hz), 5.94 (d, 1H, *J* = 9.5 Hz), 5.34 (d, 1H, *J* = 9.0 Hz), 3.73 (s, 3H), 3.27 (d, 1H, 15.0 Hz), 3.12 (d, 1H, *J* = 15.0 Hz), 3.03 (s, 3H), 2.02 (sxt, 1H, *J* = 7.5 Hz), 1.51 (sxt, 1H, *J* =7.5 Hz), 1.24 (s, 3H), 0.80 (t, 3H, *J* = 7.5 Hz). ^{13}C NMR (125 MHz, $CDCl_3$), δ: 178.5, 158.6, 141.9, 138.8, 136.8, 133.3, 128.9, 128.4, 128.3, 127.8, 127.6, 127.1, 117.6, 116.6, 113.6, 73.3, 66.1, 55.4, 49.2, 43.4, 33.8, 32.2, 23.2, 9.0. FTIR (neat), cm^{-1}: 3402 (br), 2969, 1597 (m), 1471 (m), 1384, 1240 (m). HRMS (ESI): Calcd for $(C_{28}H_{32}BrNO_3 + H)^+$: 510.1638. Found: 510.1631.



Cyclic oxazolinium triflate (120)

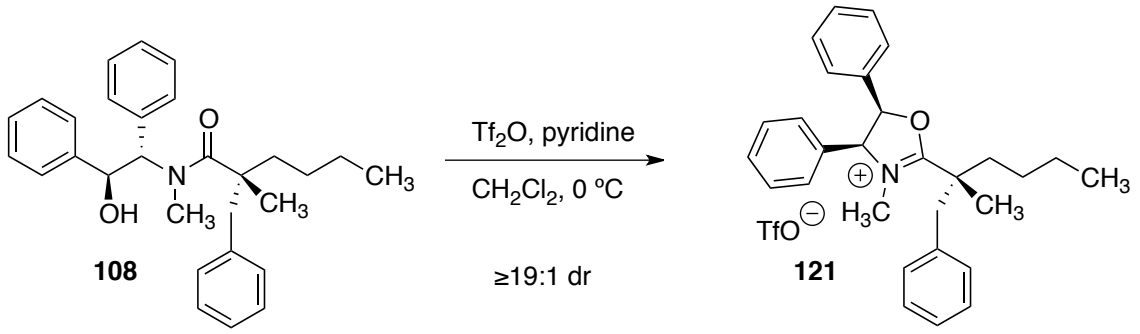
Trifluoromethanesulfonic anhydride (13.2 μL, 0.078 mmol, 2.00 equiv) was added dropwise by syringe to a stirring solution of the α-quaternary amide **107** (20.0 mg, 0.039 mmol, 1 equiv) and pyridine (9.47 μL, 0.118 mmol, 3.00 equiv) in dichloromethane (2 mL) at 0 °C. The reaction mixture was stirred for 10 min at 0 °C. The product solution was concentrated by rotary evaporation at ~40 mmHg, then with a vacuum manifold at 0.1 mmHg for 3 h. The diastereomeric ratio of the residue was determined to be ≥19:1 by ^{1}H NMR analysis. ^{1}H NMR (≥19:1 diastereomeric ratio, asterisk denotes pyridinium ion peaks, 500 MHz, $CDCl_3$), δ: 8.91* (d, 1H, *J* = 5.0 Hz), 8.56* (t, 1H, *J* = 8.0 Hz), 8.07* (t, 1H, *J* = 7.0 Hz), 7.55 (d, 1H, *J* = 9.0 Hz), 7.22-7.11 (m, 8H), 6.97-6.96 (m, 1H), 6.94 (d, 1H, *J* = 3.5 Hz), 6.90-6.87 (m,2H), 6.79, (dd, 1H, *J* = 8.5, 3.0 Hz), 6.37 (d, 1H, *J* = 10.5 Hz), 3.83 (s, 3H), 3.51 (s, 3H), 3.50 (d, 1H, *J* = 14.0 Hz), 3.44 (d, 1H, *J* = 14.0 Hz), 2.40 (sxt, 1H, *J* = 7.3 Hz), 1.85 (sxt, 1H, *J* = 7.3 Hz), 1.68 (s, 3H), 1.21 (t, 3H, *J* = 7.3 Hz).



(*R*)-2-benzyl-*N*-[(1*S*,2*S*)-2-hydroxy-1,2-diphenylethyl]-*N*,2-dimethylhexanamide (108)

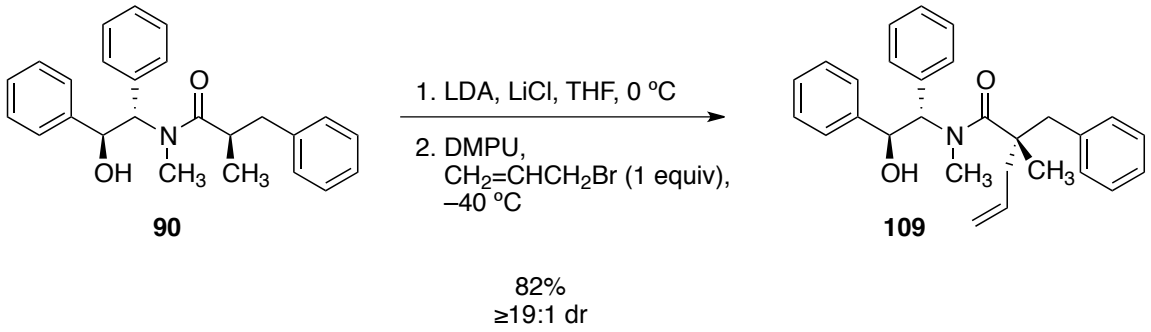
N,*N*-Diisopropylamine (161 μL, 1.15 mmol, 2.93 equiv) was added by syringe to a stirring suspension of lithium chloride (150 mg, 3.53 mmol, 9.00 equiv) in tetrahydrofuran (800 μL) at 23 ºC. The resulting slurry was cooled to –78 ºC. A freshly titrated solution of *n*-butyllithium in hexanes (2.38 M, 484 μL, 2.93 equiv) was added by syringe. The reaction mixture was warmed briefly to 0 ºC (5 min), then was cooled to –78 ºC. An ice-cooled solution of amide **91** (200 mg, 0.589 mmol, 1.50 equiv) in tetrahydrofuran (700 μL) was then added by syringe. The transfer was quantitated with tetrahydrofuran (500 μL). The reaction mixture was stirred for 3 h at 0 ºC. The yellow heterogeneous mixture was cooled to –40 ºC, then DMPU (178 μL, 1.47 mmol, 3.74 equiv) was added by syringe and stirring was continued for 15 min at –40 ºC, whereupon benzyl bromide (46.7 μL, 0.393 mmol, 1 equiv) was added by syringe. The mixture was stirred for 3.5 h at –40 ºC, then saturated aqueous ammonium chloride solution (1.5 mL) was added and the biphasic mixture was warmed to 23 ºC. The biphasic mixture was partitioned between ethyl acetate (20 mL) and a 1:1 mixture of saturated aqueous sodium chloride solution and 1 N aqueous hydrochloric acid solution (30 mL). The layers were separated. The aqueous layer was extracted with two 20-mL portions of ethyl acetate. The combined organic extracts were dried over sodium sulfate. The dried solution was

filtered, and the filtrate was concentrated. The residue was purified by flash column chromatography (10→30% ethyl acetate–hexanes) to provide amide **108** as an off-white solid (147 mg, 87%). The diastereomeric ratio of the purified product was determined to be ≥19:1 by ^{1}H NMR analysis of the corresponding cyclic oxazolinium triflate derivative (see below). TLC (40% Ethyl acetate–hexanes): R_f = 0.81 (UV, $KMnO_4$). ^{1}H NMR (500 MHz, $CDCl_3$), δ: 7.41-7.15 (m, 15H), 5.84 (d, 1H, *J* = 9.0 Hz), 5.32 (d, 1H, *J* = 9.0 Hz), 3.13 (d, 1H, *J* = 13.5 Hz), 2.81 (d, 1H, *J* = 13.5 Hz), 1.84 (dt, 1H, *J* = 13.0, 4.0 Hz), 1.34 (dt, 1H, *J* = 12.5, 4.0 Hz), 1.28-1.22 (m 2H), 1.20 (s, 3H), 1.09-1.04 (m, 2H), 0.81 (t, 3H, *J* = 7.5 Hz). ^{13}C NMR (125 MHz, $CDCl_3$), δ: 178.7, 141.9, 137.8, 136.8, 130.4, 129.1, 128.4, 128.2, 128.0, 127.7, 127.6, 127.1, 126.4, 73.2, 66.4, 48.4, 45.6, 39.4, 33.7, 26.7, 24.3, 23.3, 13.9. FTIR (neat), cm^{-1}: 3410 (br), 2956, 1601 (m), 1452, 1078, 908. HRMS (ESI): Calcd for $(C_{29}H_{35}NO_2 + H)^+$: 430.2741. Found: 430.2735.



Cyclic oxazolinium triflate (121)

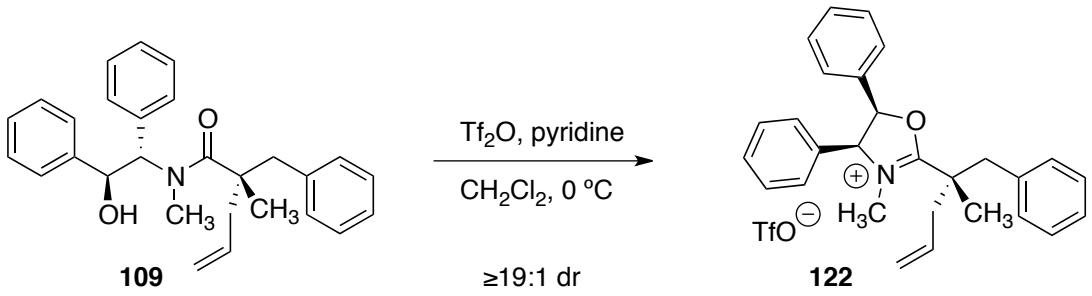
Trifluoromethanesulfonic anhydride (15.7 μL, 0.093 mmol, 2.00 equiv) was added dropwise by syringe to a stirring solution of the α-quaternary amide **108** (20.0 mg, 0.047 mmol, 1 equiv) and pyridine (11.3 μL, 0.140 mmol, 3.00 equiv) in dichloromethane (2 mL) at 0 °C. The reaction mixture was stirred for 10 min at 0 °C. The product solution was concentrated by rotary evaporation at ~40 mmHg, then with a vacuum manifold at 0.1 mmHg for 3 h. The diastereomeric ratio of the residue was determined to be ≥19:1 by ^{1}H NMR analysis. ^{1}H NMR (≥19:1 diastereomeric ratio, asterisk denotes pyridinium ion peaks, 500 MHz, $CDCl_3$), δ: 8.88* (t, 1H, *J* = 6.1 Hz), 8.56* (t, 1H, *J* = 7.7 Hz), 8.06* (t, 1H, *J* = 6.5 Hz), 7.47-7.08 (m, 14H), 6.86 (d, 1H, *J* = 6.5 Hz), 6.81 (d, 1H, *J* = 11.0 Hz), 6.37 (d, 1H, *J* = 10.5 Hz), 3.34 (s, 3H), 3.29 (d, 1H, *J* = 14.0 Hz), 3.21 (d, 1H, *J* = 14.0 Hz), 2.19 (dt, 1H, *J* = 14.0, 3.2 Hz), 1.75 (dt, 1H, *J* = 13.8, 4.3 Hz), 1.67 (s, 3H), 1.60-1.44 (m, 4H), 0.99 (t, 3H, *J* = 7.0 Hz).



(*S*)-2-benzyl-*N*-[(1*S*,2*S*)-2-hydroxy-1,2-diphenylethyl]-*N*,2-dimethylpent-4-enamide (109)

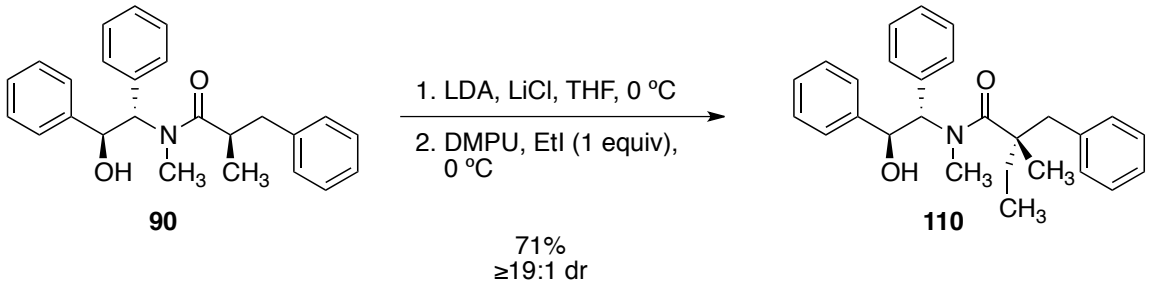
N,*N*-Diisopropylamine (110 μL, 0.785 mmol, 2.54 equiv) was added by syringe to a stirring suspension of lithium chloride (102 mg, 2.41 mmol, 7.80 equiv) in tetrahydrofuran (500 μL) at 23 ºC. The resulting slurry was cooled to –78 ºC. A freshly titrated solution of *n*-butyllithium in hexanes (2.38 M, 330 μL, 2.54 equiv) was added by syringe. The reaction mixture was warmed briefly to 0 ºC (5 min), then was cooled to –78 ºC. An ice-cooled solution of amide **90** (150 mg, 0.402 mmol, 1.30 equiv) in tetrahydrofuran (500 μL) was then added by syringe. The transfer was quantitated with tetrahydrofuran (340 μL). The reaction mixture was stirred for 3 h at 0 ºC. The yellow heterogeneous mixture was cooled to –40 ºC, then DMPU (121 μL, 1.00 mmol, 3.25 equiv) was added by syringe and stirring was continued for 15 min at –40 ºC, whereupon allyl bromide (27.0 μL, 0.309 mmol, 1 equiv) was added by syringe. The mixture was stirred for 1.3 h at –40 ºC, then saturated aqueous ammonium chloride solution (1.5 mL) was added and the biphasic mixture was warmed to 23 ºC. The biphasic mixture was partitioned between ethyl acetate (20 mL) and a 1:1 mixture of saturated aqueous sodium chloride solution and 1 N aqueous hydrochloric acid solution (30 mL). The layers were separated. The aqueous layer was extracted with two 20-mL portions of ethyl acetate.

The combined organic extracts were dried over sodium sulfate. The dried solution was filtered, and the filtrate was concentrated. The residue was purified by flash column chromatography (10→50% ethyl acetate–hexanes) to provide amide **109** as a pale-yellow semi-solid (105 mg, 82%). The diastereomeric ratio of the purified product was determined to be ≥19:1 by ^{1}H NMR analysis of the corresponding cyclic oxazolinium triflate derivative (see below). TLC (40% Ethyl acetate–hexanes): R_f = 0.72 (UV, $KMnO_4$). ^{1}H NMR (500 MHz, $CDCl_3$), δ: 7.43-7.01 (m, 15H), 5.91-5.79 (m, 2H), 5.32 (dd, 1H, *J* = 9.0, 6.0 Hz), 5.17-5.07 (m, 2H), 3.64 (d, 1H, *J* = 5.0 Hz), 3.12 (d, 1H, *J* = 14.0 Hz), 2.96 (s, 3H), 2.85-2.73 (m, 2H), 2.19 (dd, 1H, *J* = 15.0, 8.0 Hz), 1.24 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$), δ: 177.8, 141.6, 137.3, 136.4, 134.5, 130.3, 129.3, 128.3, 128.2, 128.1, 127.7, 127.6, 127.2, 126.5, 118.1, 73.0, 66.2, 48.4, 44.9, 44.6, 33.3, 24.1. FTIR (neat), cm^{-1}: 3416 (br), 3030, 1603 (m), 1452, 1076, 910. HRMS (ESI): Calcd for $(C_{28}H_{31}NO_2 + H)^+$: 414.2428. Found: 414.2426.



Cyclic oxazolinium triflate (122)

Trifluoromethanesulfonic anhydride (16.0 μL, 0.097 mmol, 2.00 equiv) was added dropwise by syringe to a stirring solution of the α-quaternary amide **109** (20.0 mg, 0.048 mmol, 1 equiv) and pyridine (12.0 μL, 0.145 mmol, 3.00 equiv) in dichloromethane (2 mL) at 0 °C. The reaction mixture was stirred for 10 min at 0 °C. The product solution was concentrated by rotary evaporation at ~40 mmHg, then with a vacuum manifold at 0.1 mmHg for 3 h. The diastereomeric ratio of the residue was determined to be ≥19:1 by ^{1}H NMR analysis. ^{1}H NMR (≥19:1 diastereomeric ratio, asterisk denotes pyridinium ion peaks, 500 MHz, $CDCl_3$), δ: 8.83* (d, 1H, *J* = 4.9 Hz), 8.42-8.29* (m, 1H), 7.89* (dd, 1H, *J* = 6.3, 7.3 Hz), 7.52-6.78 (m, 15H), 6.73 (d, 1H, *J* = 11.0 Hz), 6.38 (d, 1H, *J* = 10.5 Hz), 5.98 (m, 1H), 5.45-5.33 (m, 2H), 3.45 (s, 3H), 3.41 (d, 1H, *J* = 14.0 Hz), 3.15 (d, 1H, *J* = 14.5 Hz), 3.00 (dd, 1H, *J* = 14.5, 8.0 Hz), 2.61 (dd, 1H, *J* = 14.5, 6.5 Hz), 1.65 (s, 3H).

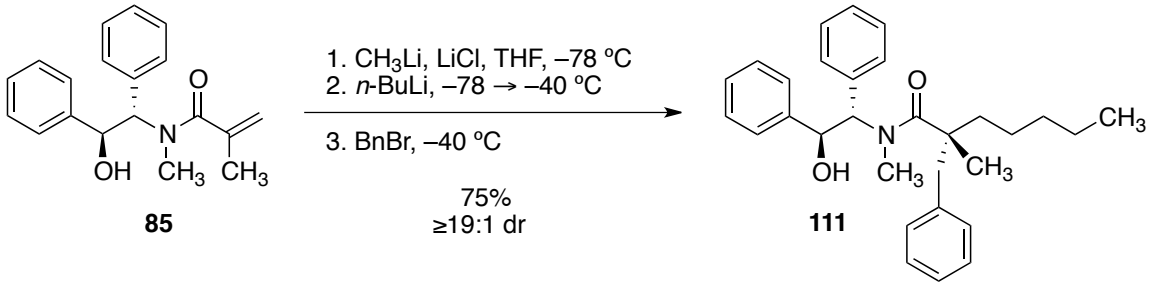


(*S*)-2-benzyl-*N*-[(1*S*,2*S*)-2-hydroxy-1,2-diphenylethyl]-*N*,2-dimethylbutanamide (110)

N,*N*-Diisopropylamine (110 μL, 0.784 mmol, 2.93 equiv) was added by syringe to a stirring suspension of lithium chloride (102 mg, 2.41 mmol, 9.00 equiv) in tetrahydrofuran (500 μL) at 23 ºC. The resulting slurry was cooled to –78 ºC. A freshly titrated solution of *n*-butyllithium in hexanes (2.38 M, 330 μL, 2.93 equiv) was added by syringe. The reaction mixture was warmed briefly to 0 ºC (5 min), then was cooled to –78 ºC. An ice-cooled solution of amide **90** (150 mg, 0.402 mmol, 1.50 equiv) in tetrahydrofuran (500 μL) was then added by syringe. The transfer was quantitated with tetrahydrofuran (340 μL). The reaction mixture was stirred for 3 h at 0 ºC. Then, DMPU (121 μL, 1.00 mmol, 3.74 equiv) was added by syringe and stirring was continued for 15 min at 0 ºC, whereupon iodoethane (21.5 μL, 0.268 mmol, 1 equiv) was added by syringe. The mixture was stirred for 18.5 h at 0 ºC, then saturated aqueous ammonium chloride solution (1.5 mL) was added and the biphasic mixture was warmed to 23 ºC. The biphasic mixture was partitioned between ethyl acetate (20 mL) and a 1:1 mixture of saturated aqueous sodium chloride solution and 1 N aqueous hydrochloric acid solution (30 mL). The layers were separated. The aqueous layer was extracted with two 20-mL portions of ethyl acetate. The combined organic extracts were dried over sodium sulfate. The dried solution was filtered, and the filtrate was concentrated. The residue was

purified by flash column chromatography (10→50% ethyl acetate–hexanes) to provide amide **110** as a yellow semi-solid (89.0 mg, 83%, mixture of diastereomers). The diastereomeric ratio of the purified product was determined to be 9.9:1 by ^{1}H NMR analysis. The diastereomers were separated by radial chromatography (10→30% ethyl acetate–hexanes) to provide amide **110** as a clear, colorless semi-solid (77.0 mg, 71%, ≥19:1 dr) and amide **105** as a white solid (6.0 mg, 6%, ≥19:1 dr). TLC (40% Ethyl acetate–hexanes): R_f = 0.65 (UV, $KMnO_4$). ^{1}H NMR (500 MHz, $CDCl_3$), δ: 7.40-7.03 (m, 15H), 5.92 (d, 1H, *J* = 9.0 Hz), 5.31 (d, 1H, *J* = 9.0 Hz), 3.73 (br, 1H), 3.09 (d, 1H, *J* = 14.0 Hz), 2.96 (s, 3H), 2.73 (d, 1H, *J* = 13.5 Hz), 2.03 (app sxt, 1H, *J* = 7.2 Hz), 1.45 (app sxt, 1H, *J* = 7.2 Hz), 1.21 (s, 3H), 0.94 (t, 3H, *J* = 7.5 Hz). ^{13}C NMR (125 MHz, $CDCl_3$), δ: 178.7, 141.9, 137.8, 136.5, 130.4, 129.4, 128.4, 128.3, 128.0, 127.7, 127.1, 126.4, 73.3, 66.0, 49.0, 44.9, 33.1, 32.8, 23.8, 9.2. FTIR (neat), cm^{-1}: 3404 (br), 2974, 1601 (s), 1452 (m), 1386, 1078 (m). HRMS (ESI): Calcd for $(C_{27}H_{31}NO_2 + H)^{+}$: 402.2428. Found: 402.2419.

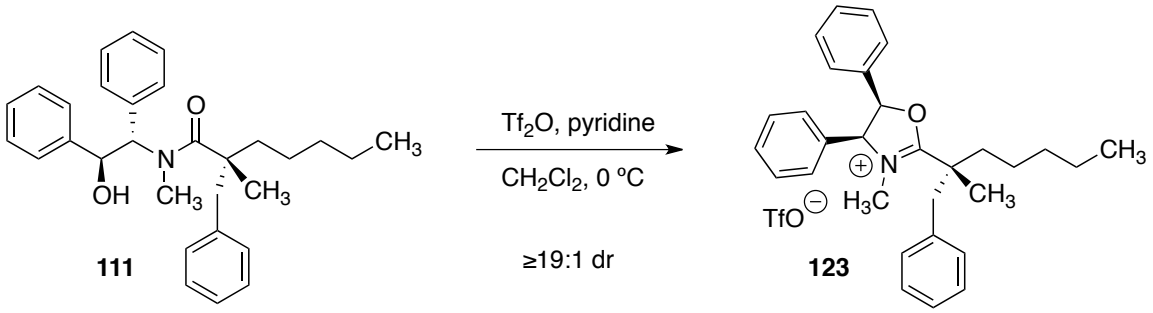
Conjugate addition–alkylation of α-alkyl-α,β-unsaturated pseudoephenamine amides depicted in Table 3.3:



(*R*)-2-benzyl-*N*-[(1*S*,2*S*)-2-hydroxy-1,2-diphenylethyl]-*N*,2-dimethylheptanamide (111)

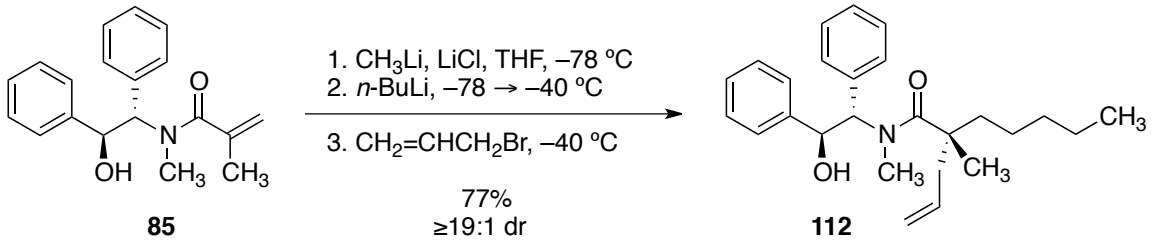
A freshly titrated solution of methyllithium in diethoxymethane (2.67 M, 630 μL, 1.00 equiv) was added by syringe to a stirring suspension of amide **85** (496 mg, 1.68 mmol, 1 equiv) and lithium chloride (428 mg, 10.1 mmol, 6.00 equiv) in tetrahydrofuran (8.40 mL) at –78 ºC. After stirring for 10 min at –78 ºC, a freshly titrated solution of *n*-butyllithium in hexanes (2.45 M, 823 μL, 1.20 equiv) was added by syringe. The resulting solution was stirred for 10 min at –78 ºC and for 10 min at –40 ºC, whereupon benzyl bromide (600 μL, 5.04 mmol, 3.00 equiv) was added by syringe. The mixture was stirred for 1 h at –40 ºC, then saturated aqueous ammonium chloride (2 mL) was added and the biphasic mixture was warmed to 23 ºC. The biphasic mixture was partitioned between ethyl acetate (60 mL) and 0.5 N aqueous hydrochloric acid solution (20 mL). The layers were separated. The organic layer was washed sequentially with 0.5 N aqueous hydrochloric acid solution (2 x 20 mL) and saturated aqueous sodium chloride solution (20 mL). The washed organic layer was dried over sodium sulfate. The dried solution was filtered, and the filtrate was concentrated. The residue was purified by flash column chromatography (5→45% ethyl acetate–hexanes) to afford amide **111** as a white,

crystalline solid (560 mg, 75%, mp = 80-82 ºC). The diastereomeric ratio of the purified product was determined to be ≥19:1 by ^{1}H NMR analysis of the corresponding cyclic oxazolinium triflate derivative (see below). TLC (40% ethyl acetate–hexanes): R_f = 0.60 (UV, $KMnO_4$). ^{1}H NMR (500 MHz, $CDCl_3$), δ: 7.40 (d, 2H, *J* = 7.3 Hz), 7.09–7.31 (m, 13H), 5.85 (d, 1H, *J* = 8.8 Hz), 5.32 (dd, 1H, *J* = 9.0, 7.1 Hz), 3.70 (d, 1H, *J* = 4.9 Hz), 3.12 (d, 1H, *J* = 13.7 Hz), 3.94 (s, 3H), 2.81 (d, 1H, *J* = 13.7 Hz), 1.83 (td, 1H, *J* = 13.1, 3.7 Hz), 1.00–1.41 (m, 11H), 0.82 (t, 3H, *J* = 7.1 Hz). ^{13}C NMR (125 MHz, $CDCl_3$), δ: 178.5, 141.9, 137.8, 136.8, 136.5, 130.4, 129.0, 128.2, 128.1, 127.9, 127.6, 127.5, 127.0, 126.3, 73.1, 66.1, 48.3, 45.5, 39.6, 33.6, 32.3, 24.3, 24.2, 22.4, 14.0. FTIR (neat), cm^{-1}: 3402 (br), 2929, 1602 (s), 1452 (m). HRMS (ESI): Calcd for $(C_{30}H_{37}NO_2 + H)^+$: 444.2897. Found: 444.2896.



Cyclic oxazolinium triflate (123)

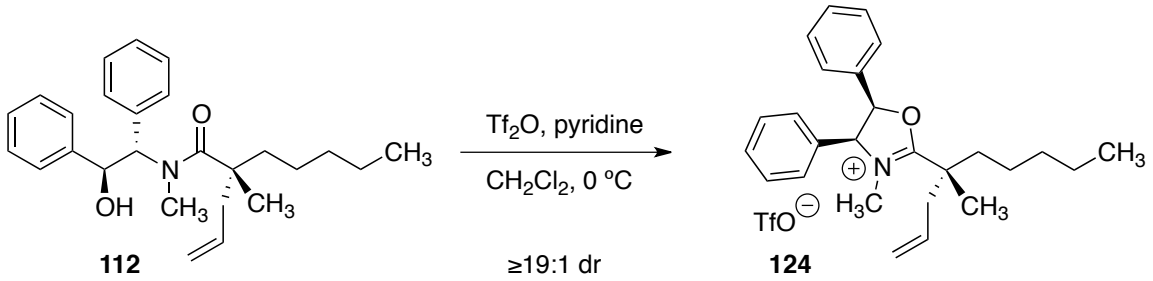
Trifluoromethanesulfonic anhydride (19.8 μL, 0.118 mmol, 2.00 equiv) was added dropwise by syringe to a stirring solution of α-quaternary amide **111** (26.1 mg, 0.059 mmol, 1 equiv) and pyridine (14.3 μL, 0.177 mmol, 3.00 equiv) in dichloromethane (2 mL) at 0 °C. The reaction mixture was stirred for 10 min at 0 °C. The product solution was concentrated by rotary evaporation at ~40 mmHg, then with a vacuum manifold at 0.1 mmHg for 2 h. The diastereomeric ratio of the residue was determined to be ≥19:1 by ^{1}H NMR analysis. ^{1}H NMR (≥19:1 diastereomeric ratio, asterisk denotes pyridinium ion peaks, 500 MHz, $CDCl_3$), δ: 8.88* (br s, 2H), 8.45* (br s, 1H), 7.98* (br d, 2H, J = 6.3 Hz), 7.46 (t, 2H, J = 7.3 Hz), 7.37 (t, 1H, J = 7.3 Hz), 7.29 (d, 2H, J = 7.3 Hz), 7.03–7.23 (m, 6H), 6.87 (d, 2H, J = 7.3 Hz), 6.76–6.84 (m, 3H), 6.36 (d, 1H, J = 11.2 Hz), 3.32 (s, 3H), 3.28 (d, 1H, J = 13.7 Hz), 3.20 (d, 1H, J = 14.2 Hz), 2.12–2.23 (m, 1H), 1.74 (td, 1H, J = 13.3, 4.6 Hz), 1.67 (s, 3H), 1.45–1.63 (m, 2H), 1.33–1.45 (m, 4H), 0.93 (t, 3H, J = 6.8 Hz).



(*R*)-2-allyl-*N*-[(1*S*,2*S*)-2-hydroxy-1,2-diphenylethyl]-*N*,2-dimethylheptanamide (112)

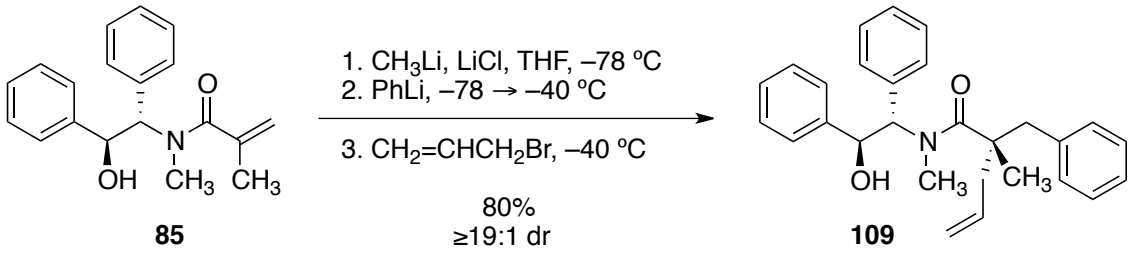
A freshly titrated solution of methyllithium in diethoxymethane (2.93 M, 610 μL, 1.00 equiv) was added by syringe to a stirring suspension of amide **85** (528 mg, 1.79 mmol, 1 equiv) and lithium chloride (455 mg, 10.7 mmol, 6.00 equiv) in tetrahydrofuran (8.93 mL) at –78 ºC. After stirring for 10 min at –78 ºC, a freshly titrated solution of *n*-butyllithium in hexanes (2.50 M, 858 μL, 1.20 equiv) was added by syringe. The resulting solution was stirred for 10 min at –78 ºC and for 10 min at –40 ºC, whereupon allyl bromide (464 μL, 5.36 mmol, 3.00 equiv) was added by syringe. The mixture was stirred for 3 h at –40 ºC, then saturated aqueous ammonium chloride (2 mL) was added and the biphasic mixture was warmed to 23 ºC. The biphasic mixture was partitioned between ethyl acetate (60 mL) and 0.5 N aqueous hydrochloric acid solution (20 mL). The layers were separated. The organic layer was washed sequentially with 0.5 N aqueous hydrochloric acid solution (2 x 20 mL) and saturated aqueous sodium chloride solution (20 mL). The washed organic layer was dried over sodium sulfate. The dried solution was filtered, and the filtrate was concentrated. The residue was purified by flash column chromatography (5→25% ethyl acetate–hexanes) to afford amide **112** as a clear, colorless oil (544 mg, 77%). The diastereomeric ratio of the purified product was determined to be ≥19:1 by ^{1}H NMR analysis of the corresponding cyclic oxazolinium triflate derivative (see below). TLC (30% ethyl acetate–hexanes): R_f = 0.48 (UV, $KMnO_4$). ^{1}H NMR (500 MHz, $CDCl_3$), δ: 7.42 (d, 2H, J = 7.3 Hz), 7.32–7.16 (m, 8H),

5.94–5.71 (m, 2H), 5.31 (dd, 1H, J = 8.8, 6.8 Hz), 5.13–5.01 (m, 2H), 3.76 (br s, 1H), 2.96 (s, 3H), 2.58 (dd, 1H, J = 14.2, 6.8 Hz), 2.23 (dd, 1H, J = 14.2, 7.3 Hz), 1.68 (td, 1H, J = 13.1, 4.2 Hz), 1.49–1.38 (m, 1H), 1.34–0.99 (m, 9H), 0.82 (t, 3H, J = 7.1 Hz). ^{13}C NMR (125 MHz, $CDCl_3$), δ: 177.7, 141.7, 137.0, 134.5, 128.6, 128.0, 127.9, 127.3, 127.2, 126.8, 117.4, 72.7, 65.4, 46.8, 43.8, 38.6, 33.4, 32.1, 24.4, 23.9, 22.2, 13.8. FTIR (neat), cm^{-1}: 3396 (br), 2927 (m), 1603 (s), 1455 (m), 1376. HRMS (ESI): Calcd for $(C_{26}H_{35}NO_2 + H)^+$: 394.2741. Found: 394.2740.



Cyclic oxazolinium triflate (124)

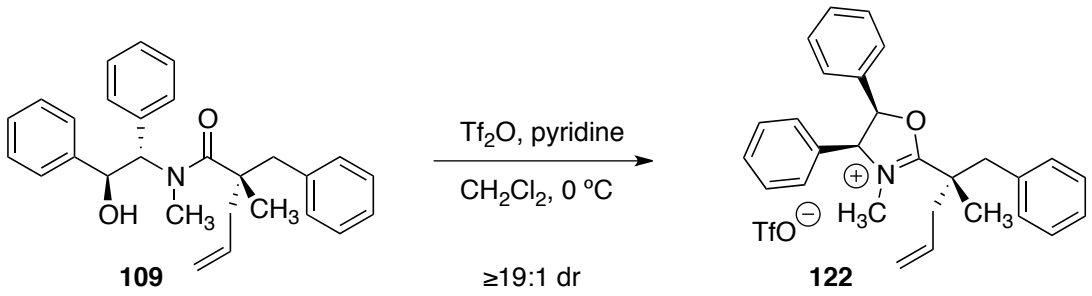
Trifluoromethanesulfonic anhydride (29.5 μL, 0.175 mmol, 2.00 equiv) was added dropwise by syringe to a stirring solution of α-quaternary amide **112** (34.5 mg, 0.088 mmol, 1 equiv) and pyridine (21.3 μL, 0.263 mmol, 3.00 equiv) in dichloromethane (2 mL) at 0 °C. The reaction mixture was stirred for 10 min at 0 °C. The product solution was concentrated by rotary evaporation at ~40 mmHg, then with a vacuum manifold at 0.1 mmHg for 2 h. The diastereomeric ratio of the residue was determined to be ≥19:1 by ^{1}H NMR analysis. ^{1}H NMR (≥19:1 diastereomeric ratio, asterisk denotes pyridinium ion peaks, 500 MHz, $CDCl_3$), δ: 8.88* (d, 2H, J = 5.4 Hz), 8.60* (t, 1H, J = 7.8 Hz), 8.10* (t, 2H, J = 7.1 Hz), 7.23–7.08 (m, 6H), 7.00–6.93 (m, 2H), 6.91 (d, 2H, J = 6.8 Hz), 6.85 (d, 1H, J = 10.7 Hz), 6.30 (d, 1H, J = 10.7 Hz), 5.98–5.86 (m, 1H), 5.40–5.27 (m, 2H), 3.48 (s, 3H), 2.78 (dd, 1H, J = 14.4, 7.6 Hz), 2.62 (dd, 1H, J = 14.4, 7.1 Hz), 2.12–1.99 (m, 1H), 1.85–1.71 (m, 1H), 1.64 (s, 3H), 1.57–1.46 (m, 2H), 1.45–1.30 (m, 4H), 0.92 (t, 3H, J = 6.8 Hz).



(*S*)-2-benzyl-*N*-[(1*S*,2*S*)-2-hydroxy-1,2-diphenylethyl]-*N*,2-dimethylpent-4-enamide (109)

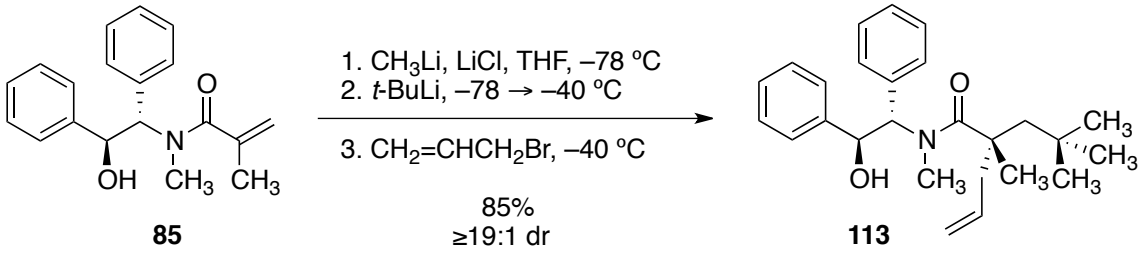
A freshly titrated solution of methyllithium in diethoxymethane (2.67 M, 629 μL, 1.00 equiv) was added by syringe to a stirring suspension of amide **85** (496 mg, 1.68 mmol, 1 equiv) and lithium chloride (427 mg, 10.1 mmol, 6.00 equiv) in tetrahydrofuran (8.40 mL) at –78 ºC. After stirring for 10 min at –78 ºC, a freshly titrated solution of phenyllithium in di-*n*-butyl ether (1.61 M, 1.23 mL, 1.20 equiv) was added by syringe. The resulting solution was stirred for 10 min at –78 ºC and for 10 min at –40 ºC, whereupon allyl bromide (436 μL, 5.04 mmol, 3.00 equiv) was added by syringe. The mixture was stirred for 6 h at –40 ºC, then saturated aqueous ammonium chloride (2 mL) was added and the biphasic mixture was warmed to 23 ºC. The biphasic mixture was partitioned between ethyl acetate (25 mL) and half-saturated aqueous sodium chloride solution (50 mL). The layers were separated. The aqueous layer was extracted with two 25-mL portions of ethyl acetate. The combined organic extracts were dried over sodium sulfate. The dried solution was filtered, and the filtrate was concentrated. The residue was purified by flash column chromatography (5→40% ethyl acetate–hexanes) to afford amide **109** as a clear, colorless glaze (556 mg, 80%). The diastereomeric ratio of the purified product was determined to be ≥19:1 by ^{1}H NMR analysis of the corresponding cyclic oxazolinium triflate derivative (see below). TLC (40% ethyl acetate–hexanes): R_f

= 0.49 (UV, $KMnO_4$). ^1H NMR (500 MHz, $CDCl_3$), δ: 7.39 (d, 3H, *J* = 7.3 Hz), 7.12–7.33 (m, 9H), 6.98–7.07 (m, 3H), 5.75–5.93 (m, 2H), 5.31 (dd, 1H, *J* = 9.3, 6.4 Hz), 5.05–5.18 (m, 2H), 3.64 (br s, 1H), 3.11 (d, 1H, *J* = 14.2 Hz), 2.95 (s, 3H), 2.70–2.84 (m, 2H), 2.18 (dd, 1H, *J* = 14.7, 7.3 Hz), 2.01–2.08 (m, 1H), 1.23 (s, 1H). ^{13}C NMR (125 MHz, $CDCl_3$), δ: 177.5, 141.6, 137.2, 136.4, 134.3, 130.2, 129.1, 128.1, 128.1, 127.9, 127.5, 127.4, 127.0, 126.3, 117.9, 72.8, 65.8, 48.2, 44.7, 44.3, 33.1, 23.9. FTIR (neat), cm^{-1}: 3406 (br), 3030, 1602 (s), 1452 (m). HRMS (ESI): Calcd for $(C_{28}H_{31}NO_2 + H)^+$: 414.2428. Found: 414.2421.



Cyclic oxazolinium triflate (122)

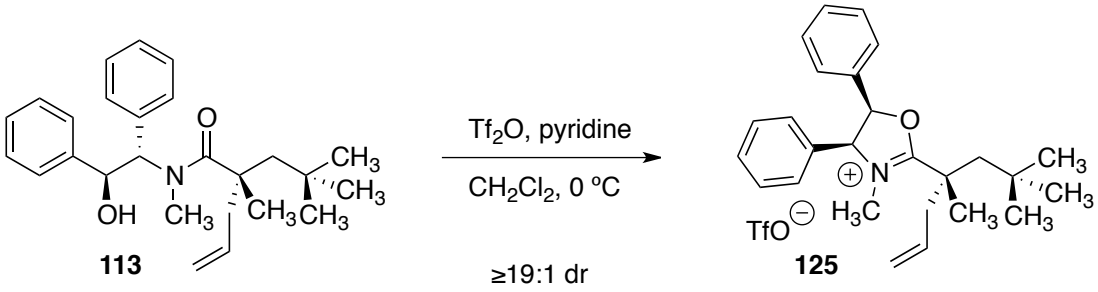
Trifluoromethanesulfonic anhydride (22.5 μL, 0.133 mmol, 2.00 equiv) was added dropwise by syringe to a stirring solution of α-quaternary amide **109** (27.6 mg, 0.067 mmol, 1 equiv) and pyridine (16.2 μL, 0.200 mmol, 3.00 equiv) in dichloromethane (2 mL) at 0 °C. The reaction mixture was stirred for 10 min at 0 °C. The product solution was concentrated by rotary evaporation at ~40 mmHg, then with a vacuum manifold at 0.1 mmHg for 2 h. The diastereomeric ratio of the residue was determined to be ≥19:1 by ^{1}H NMR analysis. ^{1}H NMR (≥19:1 diastereomeric ratio, asterisk denotes pyridinium ion peaks, 500 MHz, $CDCl_3$), δ: 8.82* (br s, 2H), 8.27* (br s, 1H), 7.83* (br s, 2H), 7.43 (t, 2H, *J* = 7.3 Hz), 7.29–7.39 (m, 3H), 7.15–7.21 (m, 1H), 7.06–7.15 (m, 5H), 6.77–6.92 (m, 4H), 6.66 (d, 1H, *J* = 10.7 Hz), 6.32 (d, 1H, *J* = 11.2 Hz), 5.91–6.04 (m, 1H), 5.32–5.44 (m, 2H), 3.45 (s, 3H), 3.40 (d, 1H, *J* = 13.7 Hz), 3.15 (d, 1H, *J* = 14.2 Hz), 3.02 (dd, 1H, *J* = 14.6, 7.9 Hz), 2.59 (dd, 1H, *J* = 14.9, 6.6 Hz), 1.63 (s, 3H).



(*S*)-*N*-[(1*S*,2*S*)-2-hydroxy-1,2-diphenylethyl]-*N*,2-dimethyl-2-neopentylpent-4-enamide (113)

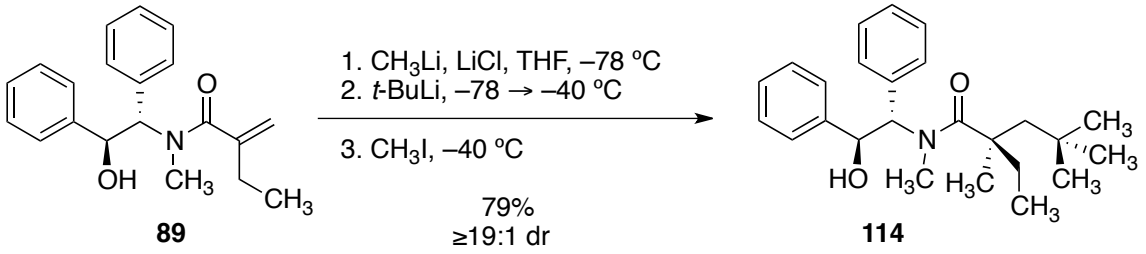
A freshly titrated solution of methyllithium in diethoxymethane (2.67 M, 250 μL, 1.00 equiv) was added by syringe to a stirring suspension of amide **85** (197 mg, 0.669 mmol, 1 equiv) and lithium chloride (170 mg, 4.01 mmol, 6.00 equiv) in tetrahydrofuran (3.34 mL) at –78 ºC. After stirring for 10 min at –78 ºC, a freshly titrated solution of *tert*-butyllithium in pentane (1.71 M, 469 μL, 1.20 equiv) was added by syringe. The resulting solution was stirred for 10 min at –78 ºC and for 10 min at –40 ºC, whereupon allyl bromide (174 μL, 2.01 mmol, 3.00 equiv) was added by syringe. The mixture was stirred for 6 h at –40 ºC, then saturated aqueous ammonium chloride (2 mL) was added and the biphasic mixture was warmed to 23 ºC. The biphasic mixture was partitioned between ethyl acetate (60 mL) and 0.5 N aqueous hydrochloric acid solution (20 mL). The layers were separated. The organic layer was washed sequentially with 0.5 N aqueous hydrochloric acid solution (2 x 20 mL) and saturated aqueous sodium chloride solution (20 mL). The washed organic layer was dried over sodium sulfate. The dried solution was filtered, and the filtrate was concentrated. The residue was purified by flash column chromatography (5→45% ethyl acetate–hexanes) to afford amide **113** as a white, crystalline solid (224 mg, 85%, mp = 90-92 ºC). The diastereomeric ratio of the purified product was determined to be ≥19:1 by ^{1}H NMR analysis of the corresponding cyclic

oxazolinium triflate derivative (see below). TLC (40% ethyl acetate–hexanes): R_f = 0.48 (UV, $KMnO_4$). ^1H NMR (500 MHz, $CDCl_3$), δ: 7.37 (d, 2H, *J* = 7.3 Hz), 7.12–7.28 (m, 8H), 6.04 (d, 1H, *J* = 9.8 Hz), 5.89 (ddt, 1H, *J* = 17.1, 10.0, 7.0, 7.0 Hz), 5.27 (dd, 1H, *J* = 10.0, 5.6 Hz), 5.06–5.19 (m, 2H), 3.36 (d, 1H, *J* = 4.9 Hz), 3.06 (s, 3H), 2.68 (dd, 1H, *J* = 14.4, 7.0 Hz), 2.21 (dd, 1H, *J* = 14.4, 7.1 Hz), 1.87 (d, 1H, *J* = 15.1 Hz), 1.46 (d, 1H, *J* = 15.1 Hz), 1.37 (s, 3H), 0.85 (s, 9H). ^{13}C NMR (125 MHz, $CDCl_3$), δ: 178.3, 141.4, 135.8, 134.6, 129.6, 128.2, 128.0, 127.6, 127.4, 117.9, 72.9, 65.1, 52.1, 48.0, 46.4, 32.5, 32.0, 31.2, 26.7. FTIR (neat), cm^{-1}: 3394 (br), 2951, 1599 (s), 1454 (m). HRMS (ESI): Calcd for $(C_{26}H_{35}NO_2 + H)^+$: 394.2741. Found: 394.2735.



Cyclic oxazolinium triflate (125)

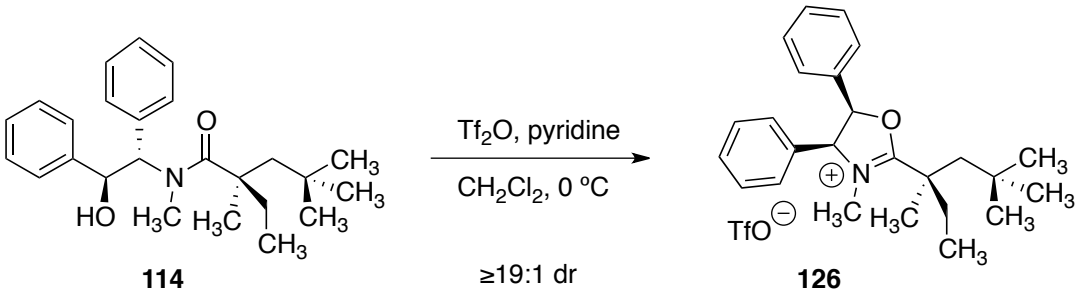
Trifluoromethanesulfonic anhydride (22.4 μL, 0.133 mmol, 2.00 equiv) was added dropwise by syringe to a stirring solution of α-quaternary amide **113** (26.2 mg, 0.067 mmol, 1 equiv) and pyridine (16.2 μL, 0.200 mmol, 3.00 equiv) in dichloromethane (2 mL) at 0 °C. The reaction mixture was stirred for 10 min at 0 °C. The product solution was concentrated by rotary evaporation at ~40 mmHg, then with a vacuum manifold at 0.1 mmHg for 2 h. The diastereomeric ratio of the residue was determined to be ≥19:1 by ^{1}H NMR analysis. ^{1}H NMR (asterisk denotes pyridinium ion peaks, 500 MHz, $CDCl_3$), δ: 8.84* (d, 2H, *J* = 5.3 Hz), 8.54* (t, 1H, *J* = 7.8 Hz), 8.04* (t, 2H, *J* = 7.0 Hz), 7.10–7.21 (m, 6H), 7.00 (d, 4H, *J* = 5.3 Hz), 6.76 (d, 1H, *J* = 11.1 Hz), 6.46 (d, 1H, *J* = 11.4 Hz), 5.88–6.00 (m, 1H), 5.32–5.43 (m, 2H), 3.49 (s, 3H), 2.83 (dd, 1H, *J* = 14.6, 8.2 Hz), 2.59 (dd, 1H, *J* = 14.6, 6.2 Hz), 2.24 (d, 1H, *J* = 15.2 Hz), 1.78 (d, 1H, *J* = 15.2 Hz), 1.74 (s, 3H), 1.13 (s, 9H).



(*R*)-2-ethyl-*N*-[(1*S*,2*S*)-2-hydroxy-1,2-diphenylethyl]-*N*,2,4,4-tetramethylpentanamide (114)

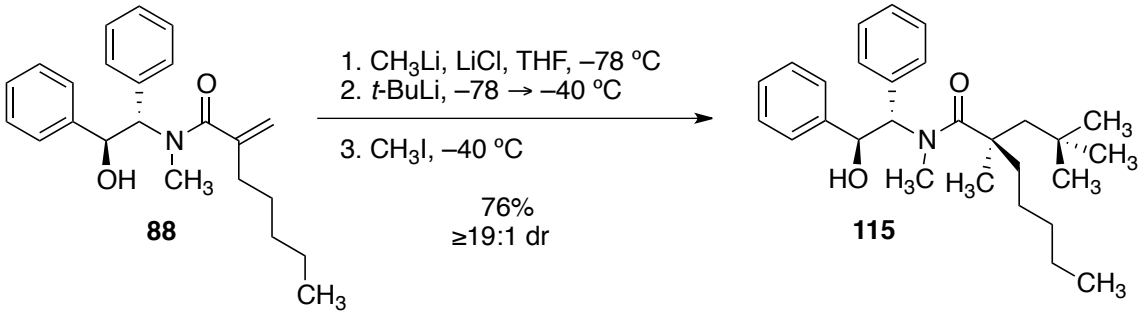
A freshly titrated solution of methyllithium in diethoxymethane (2.84 M, 569 μL, 1.00 equiv) was added by syringe to a stirring suspension of amide **89** (500 mg, 1.62 mmol, 1 equiv) and lithium chloride (411 mg, 9.70 mmol, 6.00 equiv) in tetrahydrofuran (8.08 mL) at –78 °C. After stirring for 10 min at –78 °C, a freshly titrated solution of *tert*-butyllithium in pentane (1.41 M, 1.37 mL, 1.20 equiv) was added by syringe. The resulting solution was stirred for 10 min at –78 °C and for 10 min at –40 °C, whereupon iodomethane (404 μL, 6.46 mmol, 4.00 equiv) was added by syringe. The mixture was stirred for 4 h at –40 °C, then saturated aqueous ammonium chloride (2 mL) was added and the biphasic mixture was warmed to 23 °C. The biphasic mixture was partitioned between ethyl acetate (50 mL) and half-saturated aqueous sodium chloride solution (75 mL). The layers were separated. The aqueous layer was extracted with two 50-mL portions of ethyl acetate. The combined organic extracts were dried over sodium sulfate. The dried solution was filtered, and the filtrate was concentrated. The residue was purified by flash column chromatography (5→35% ethyl acetate–hexanes) to afford amide **114** as an off-white solid (487 mg, 79%, mp = 85-86 °C). The diastereomeric ratio of the purified product was determined to be ≥19:1 by ^{1}H NMR analysis of the corresponding cyclic oxazolinium triflate derivative (see below). TLC (30% ethyl

acetate–hexanes): R_f = 0.46 (UV, $KMnO_4$). ^{1}H NMR (500 MHz, $CDCl_3$), δ: 7.37 (d, 2H, *J* = 7.3 Hz), 7.29–7.24 (m, 2H), 7.24–7.12 (m, 6H), 5.91 (d, 1H, *J* = 9.8 Hz), 5.31 (dd, 1H, *J* = 9.8, 6.4 Hz), 3.89 (d, 1H, *J* = 6.4 Hz), 3.01 (s, 3H), 1.93 (d, 1H, *J* = 14.7 Hz), 1.82 (dq, 1H, *J* = 14.3, 7.3 Hz), 1.48 (d, 1H, *J* = 15.1 Hz), 1.43–1.30 (m, 4H), 0.99 (s, 9H), 0.72 (t, 3H, *J* = 7.8 Hz). ^{13}C NMR (125 MHz, $CDCl_3$), δ: 179.7, 142.0, 136.4, 129.6, 128.2, 128.1, 127.6, 127.5, 127.2, 73.5, 66.1, 52.9, 48.3, 34.2, 33.4, 32.1, 31.4, 25.6, 8.5. FTIR (neat), cm^{-1}: 3374 (br), 2923 (s), 2853 (m), 1741 (m), 1602 (m). HRMS (ESI): Calcd for $(C_{25}H_{35}NO_2 + Na)^+$: 404.2560. Found: 404.2560.



Cyclic oxazolinium triflate (126)

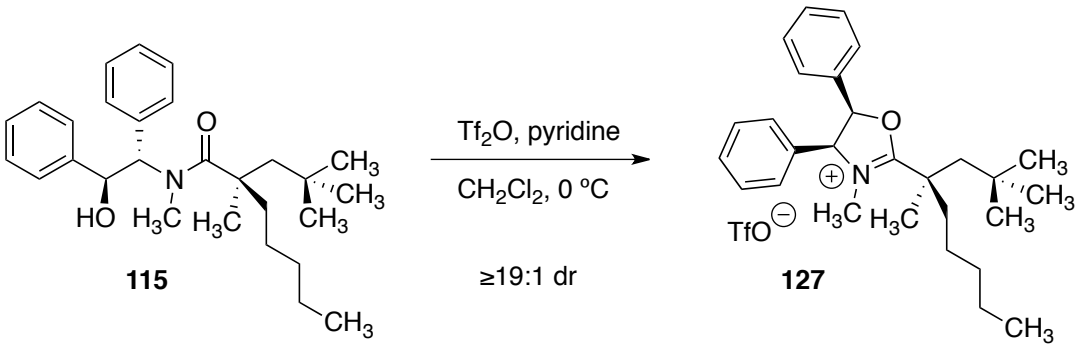
Trifluoromethanesulfonic anhydride (21.5 μL, 0.128 mmol, 2.00 equiv) was added dropwise by syringe to a stirring solution of α-quaternary amide **114** (24.4 mg, 0.064 mmol, 1 equiv) and pyridine (15.5 μL, 0.192 mmol, 3.00 equiv) in dichloromethane (2 mL) at 0 °C. The reaction mixture was stirred for 10 min at 0 °C. The product solution was concentrated by rotary evaporation at ~40 mmHg, then with a vacuum manifold at 0.1 mmHg for 2 h. The diastereomeric ratio of the residue was determined to be ≥19:1 by ^{1}H NMR analysis. ^{1}H NMR (asterisk denotes pyridinium ion peaks, 600 MHz, $CDCl_3$), δ: 8.85* (d, 2H, *J* = 5.3 Hz), 8.64–8.57* (m, 1H), 8.10* (t, 2H, *J* = 6.7 Hz), 7.23–7.16 (m, 3H), 7.16–7.10 (m, 3H), 7.01 (dd, 2H, *J* = 6.3, 2.3 Hz, 2H), 6.94 (d, 2H, *J* = 6.2 Hz), 6.75 (d, 1H, *J* = 10.8 Hz), 6.45 (d, 1H, *J* = 10.8 Hz), 3.53 (s, 3H), 2.25 (dq, 1H, *J* = 14.2, 7.3 Hz), 2.07 (d, 1H, *J* = 15.2 Hz), 1.91 (dq, 1H, *J* = 14.1, 7.3 Hz), 1.85 (d, 1H, *J* = 14.9 Hz), 1.69 (s, 3H), 1.18 (t, 3H, *J* = 7.5 Hz), 1.10 (s, 9H).



(*R*)-*N*-[(1*S*,2*S*)-2-hydroxy-1,2-diphenylethyl]-*N*,2-dimethyl-2-neopentylheptanamide (115)

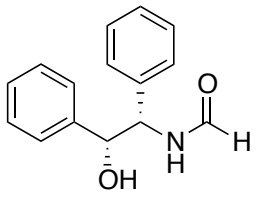
A freshly titrated solution of methyllithium in diethoxymethane (2.84 M, 501 μL, 1.00 equiv) was added by syringe to a stirring suspension of amide **88** (500 mg, 1.42 mmol, 1 equiv) and lithium chloride (362 mg, 8.54 mmol, 6.00 equiv) in tetrahydrofuran (7.11 mL) at –78 ºC. After stirring for 10 min at –78 ºC, a freshly titrated solution of *tert*-butyllithium in pentane (1.41 M, 1.21 mL, 1.20 equiv) was added by syringe. The resulting solution was stirred for 10 min at –78 ºC and for 10 min at –40 ºC, whereupon iodomethane (445 μL, 7.11 mmol, 5.00 equiv) was added by syringe. The mixture was stirred for 6 h at –40 ºC, then saturated aqueous ammonium chloride (2 mL) was added and the biphasic mixture was warmed to 23 ºC. The biphasic mixture was partitioned between ethyl acetate (50 mL) and half-saturated aqueous sodium chloride solution (75 mL). The layers were separated. The aqueous layer was extracted with two 50-mL portions of ethyl acetate. The combined organic extracts were dried over sodium sulfate. The dried solution was filtered, and the filtrate was concentrated. The residue was purified by flash column chromatography (5→35% ethyl acetate–hexanes) to afford amide **115** as an off-white solid (461 mg, 76%, mp = 99-101 ºC). The diastereomeric ratio of the purified product was determined to be ≥19:1 by ^{1}H NMR analysis of the

corresponding cyclic oxazolinium triflate derivative (see below). TLC (30% ethyl acetate–hexanes): R_f = 0.55 (UV, $KMnO_4$). ^{1}H NMR (500 MHz, $CDCl_3$), δ: 7.37 (d, 2H, *J* = 7.3 Hz), 7.30–7.11 (m, 8H), 5.94 (d, 1H, *J* = 10.3 Hz), 5.30 (dd, 1H, *J* = 9.8, 6.4 Hz, 1H), 3.85 (d, 1H, *J* = 6.4 Hz, 1H), 3.00 (s, 3H), 1.94 (d, 1H, *J* = 14.7 Hz), 1.77–1.66 (m, 1H), 1.48 (d, 1H, *J* = 15.1 Hz), 1.37 (s, 3H), 1.34–1.03 (m, 6H), 0.99 (s, 9H), 0.95–0.85 (m, 1H), 0.79 (t, 3H, *J* = 7.1 Hz). ^{13}C NMR (125 MHz, $CDCl_3$), δ: 179.8, 142.0, 136.4, 129.6, 128.2, 128.0, 127.6, 127.5, 127.2, 73.4, 65.9, 53.2, 48.1, 41.8, 33.2, 32.4, 32.1, 31.4, 26.4, 23.6, 22.5, 14.0. FTIR (neat), cm^{-1}: 3350 (br), 2959 (m), 2934 (m), 1679 (m), 1608 (s). HRMS (ESI): Calcd for $(C_{28}H_{41}NO_2 + H)^+$: 424.3210. Found: 424.3211.



Cyclic oxazolinium triflate (127)

Trifluoromethanesulfonic anhydride (19.1 μL, 0.114 mmol, 2.00 equiv) was added dropwise by syringe to a stirring solution of α-quaternary amide **115** (24.1 mg, 0.057 mmol, 1 equiv) and pyridine (13.8 μL, 0.171 mmol, 3.00 equiv) in dichloromethane (2 mL) at 0 °C. The reaction mixture was stirred for 10 min at 0 °C. The product solution was concentrated by rotary evaporation at ~40 mmHg, then with a vacuum manifold at 0.1 mmHg for 2 h. The diastereomeric ratio of the residue was determined to be ≥19:1 by ^{1}H NMR analysis. ^{1}H NMR (≥19:1 diastereomeric ratio, asterisk denotes pyridinium ion peaks, 500 MHz, $CDCl_3$), δ: 8.90* (d, 2H, *J* = 5.9 Hz), 8.85* (t, 2H, *J* = 5.9 Hz), 8.60* (t, 1H, *J* = 7.8 Hz), 8.42* (t, 1H, *J* = 7.8 Hz, 1H), 8.09* (t, 2H, *J* = 6.8 Hz), 8.01* (t, 2H, *J* = 6.8 Hz), 7.24–7.10 (m, 6H), 7.04–6.97 (m, 2H), 6.93 (d, 2H, *J* = 6.4 Hz), 6.72 (d, 1H, *J* = 10.7 Hz), 6.41 (d, 1H, *J* = 10.7 Hz), 3.53 (s, 3H), 2.20–2.01 (m, 2H), 1.92–1.77 (m, 2H), 1.71 (s, 3H), 1.64–1.51 (m, 1H), 1.49–1.33 (m, 5H), 1.10 (s, 9H), 0.93 (t, 3H, *J* = 6.6 Hz).


O
N
H
H
OH

38

8.5
8.0
7.5
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6.5
6.0
5.5
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3.5
3.0
2.5
2.0
1.5
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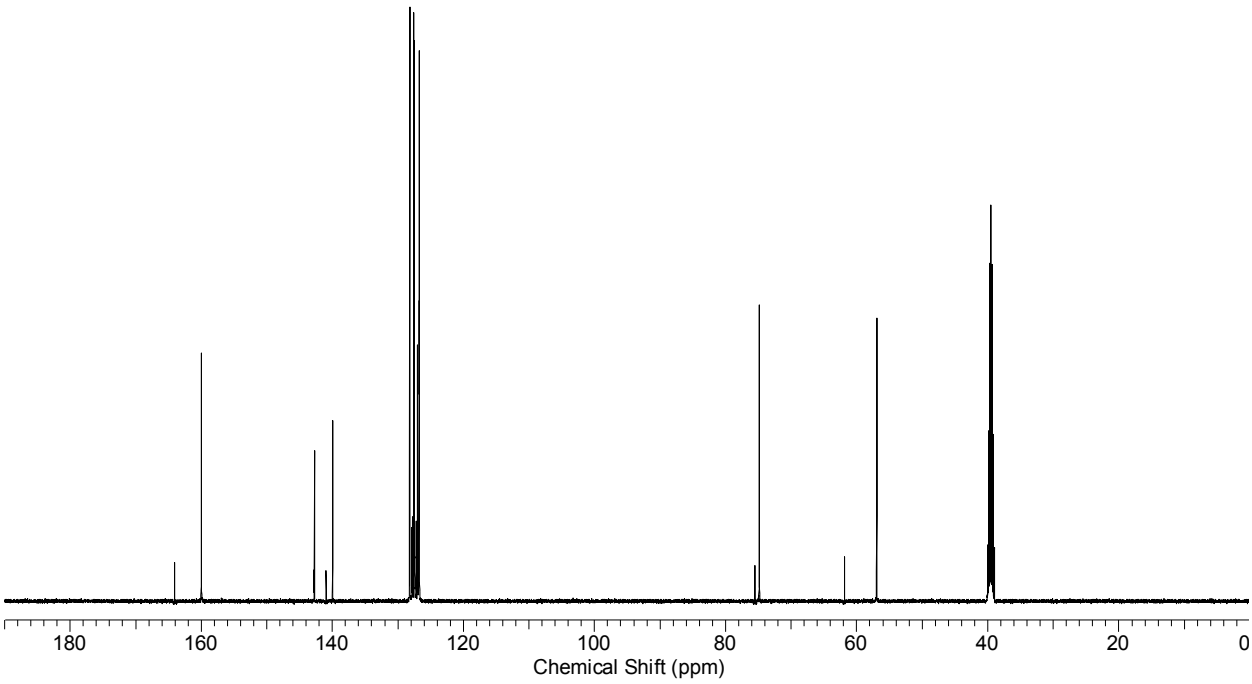
Chemical Shift (ppm)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80
60
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20
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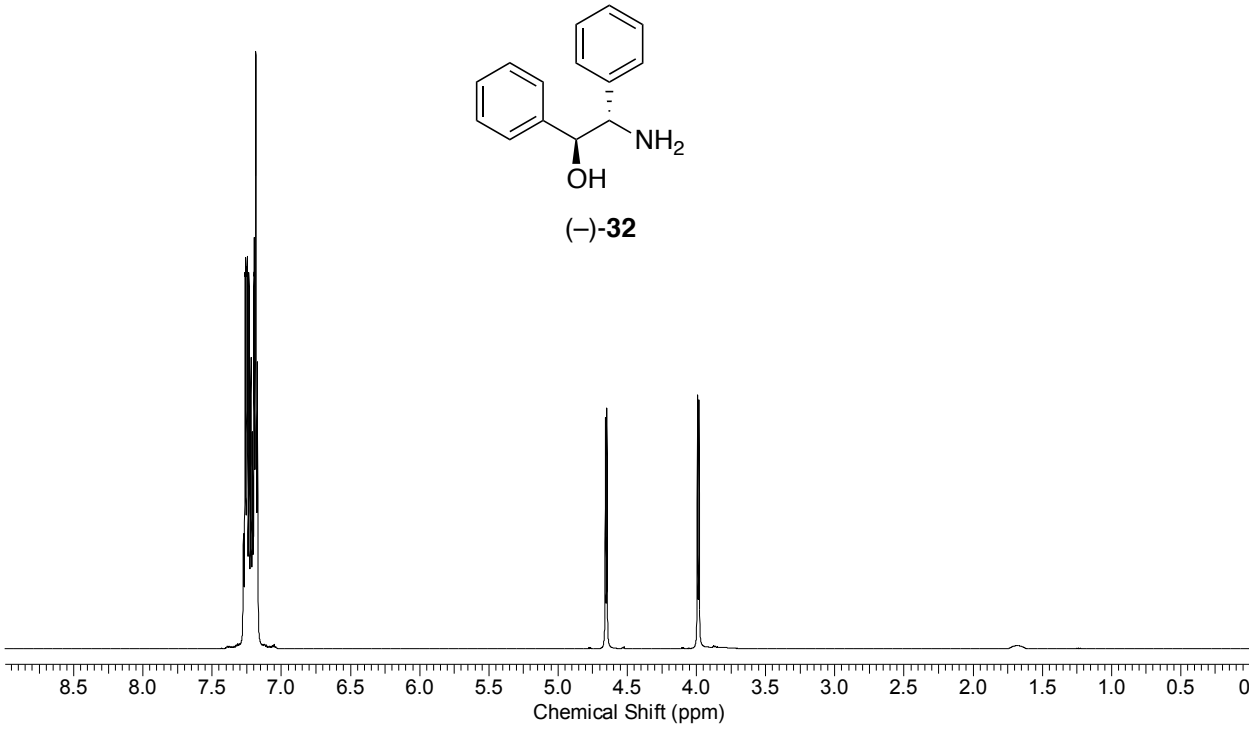
Chemical Shift (ppm)


NH2
OH
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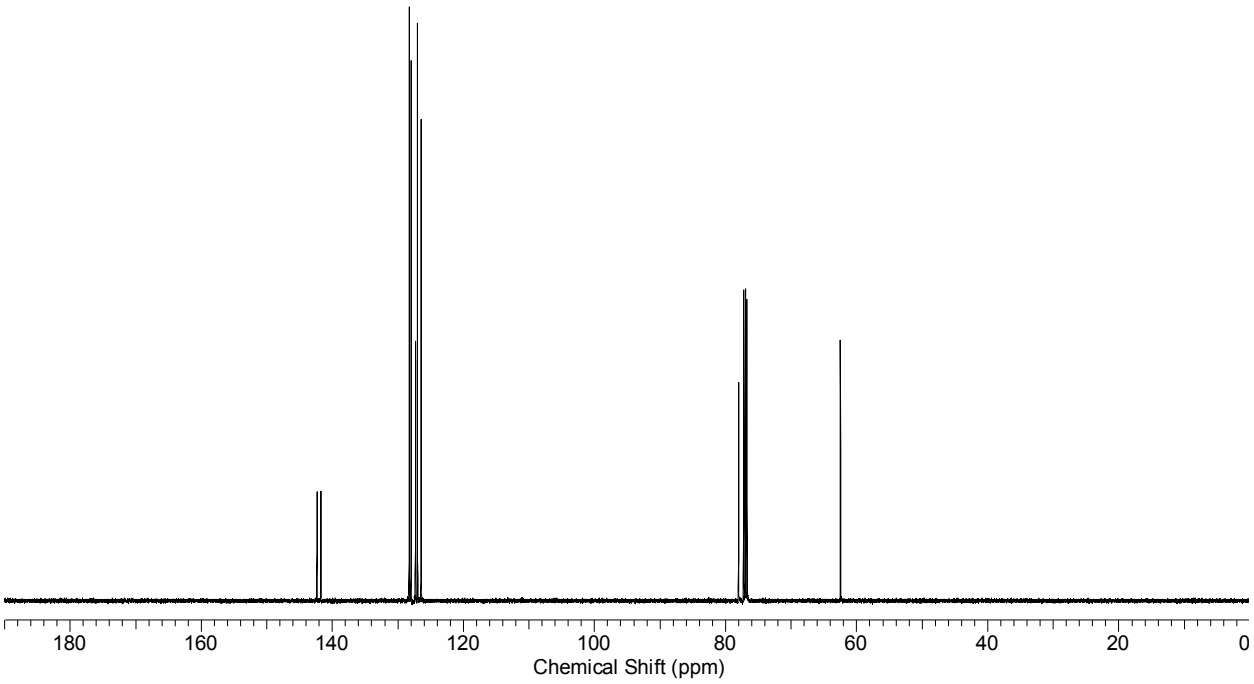
Chemical Shift (ppm)

(–)-**32**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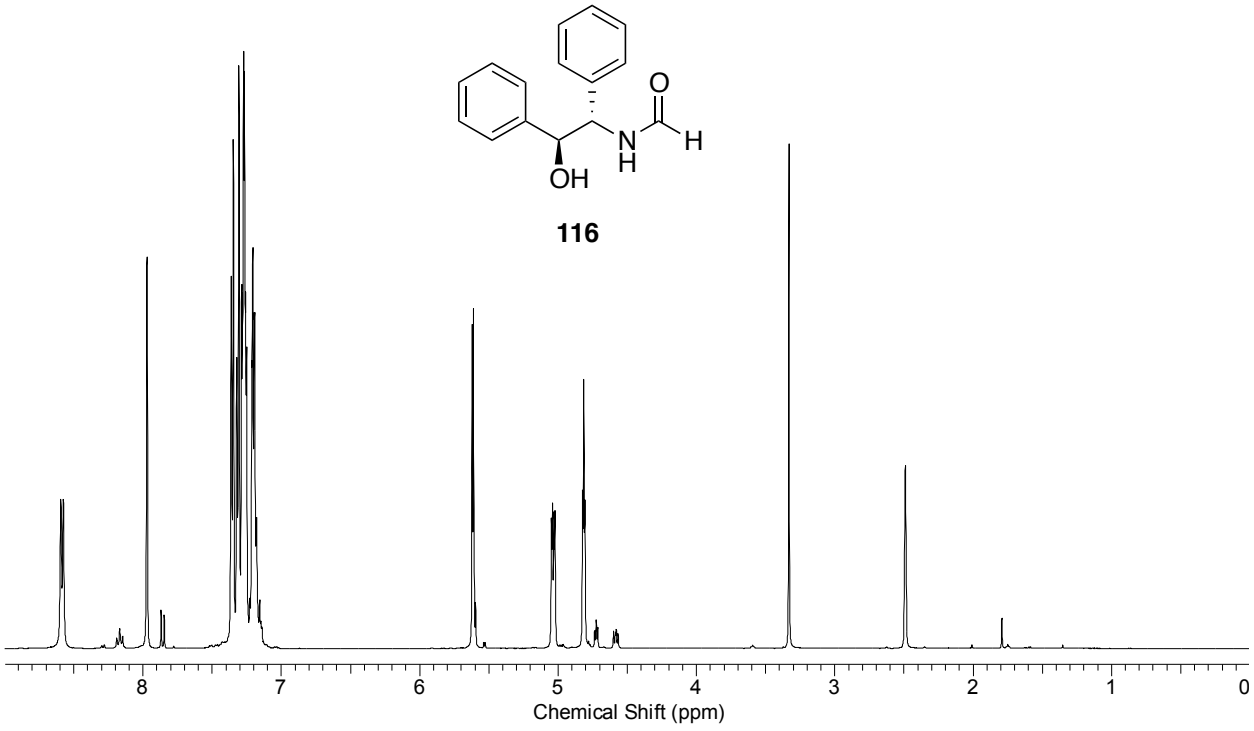
Chemical Shift (ppm)


O
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OH
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7
6
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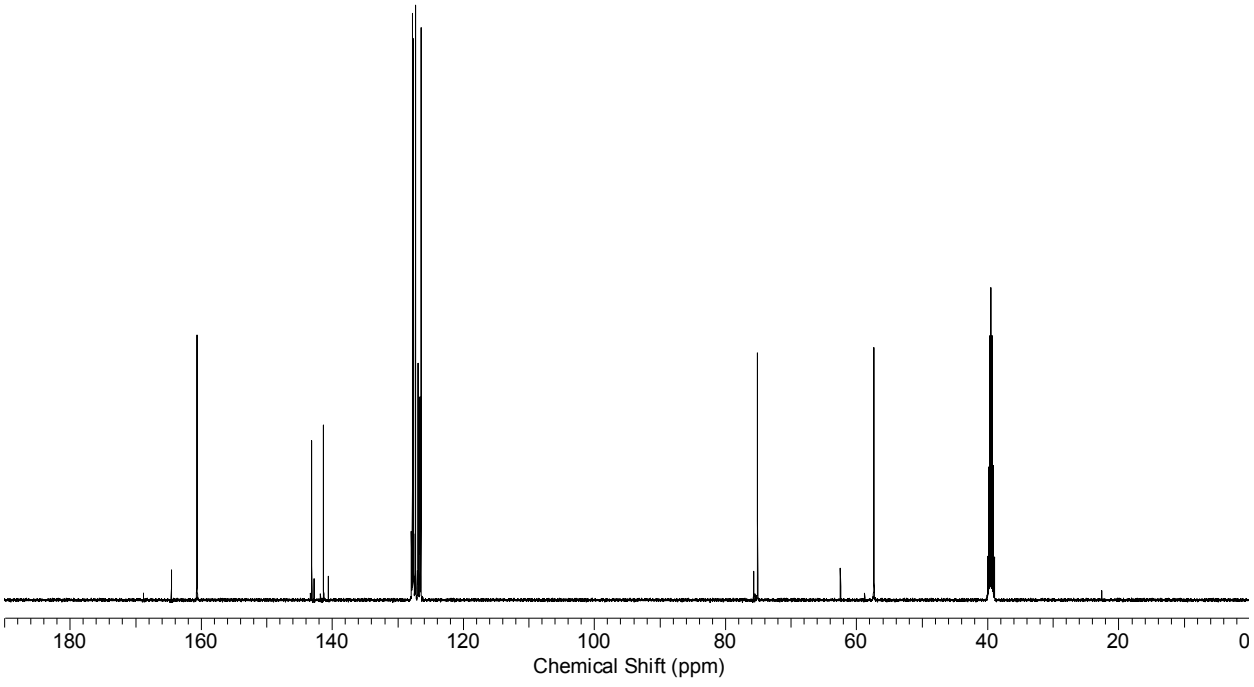
4
3
2
1
0
Chemical Shift (ppm)

116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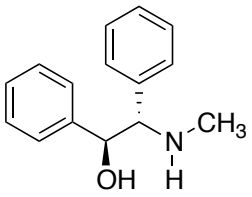
Chemical Shift (ppm)


CH3
N
H
OH

(–)-**30**

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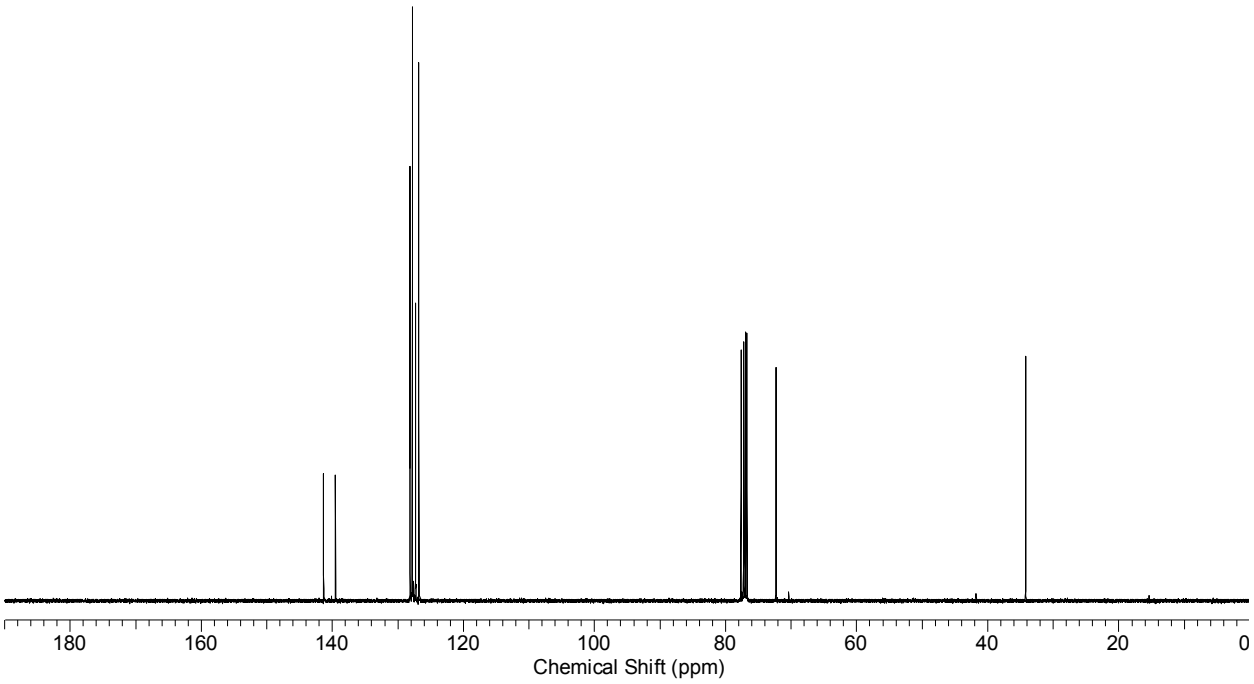
Chemical Shift (ppm)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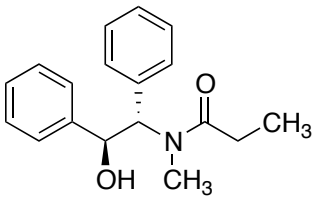
Chemical Shift (ppm)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OH
CH3

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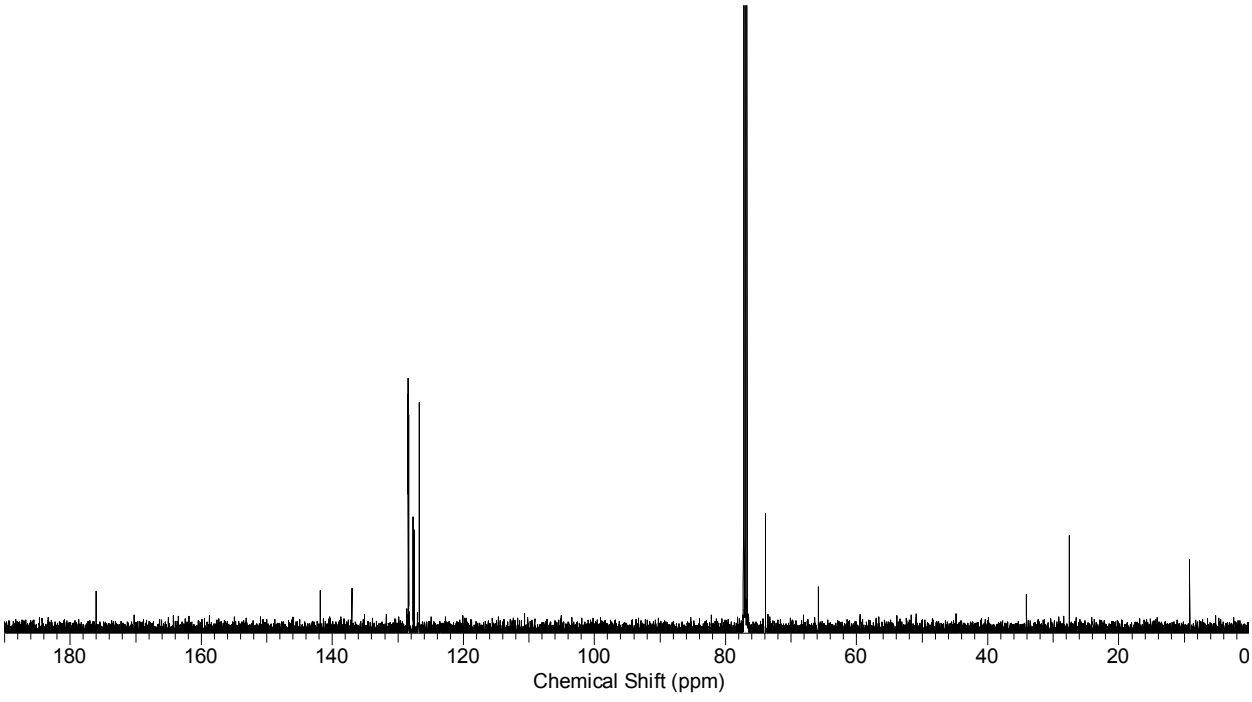
0
Chemical Shift (ppm)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100
80
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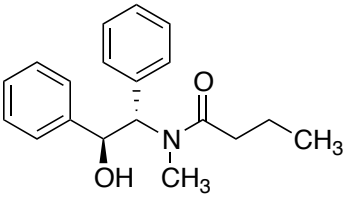
40
20
0
Chemical Shift (ppm)


O
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CH3
OH
CH3

84

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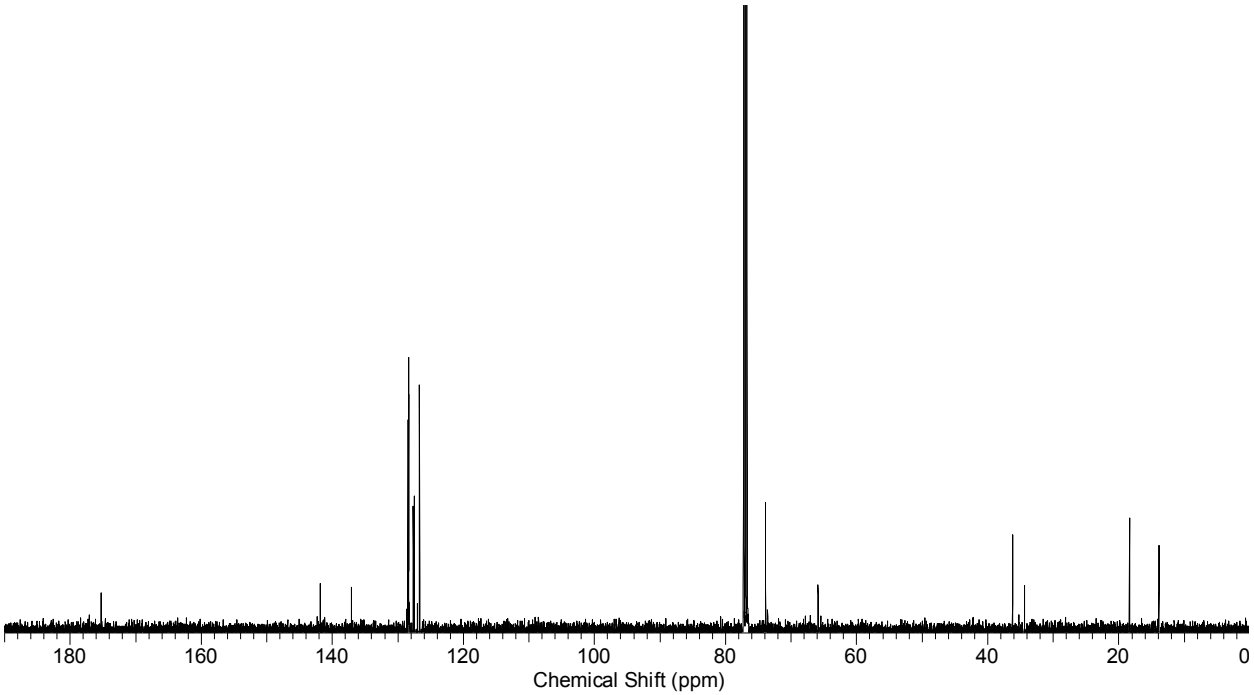
7
6
5
4
3
2
1
0
Chemical Shift (ppm)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40
20
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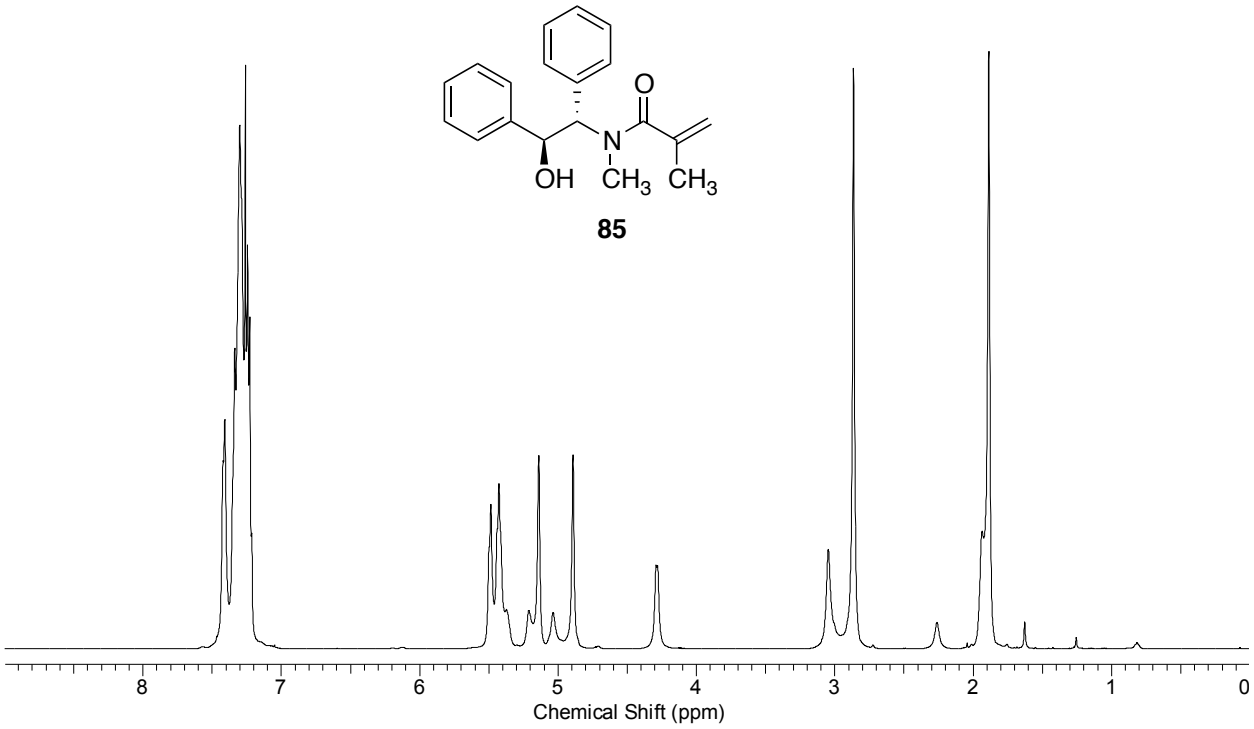
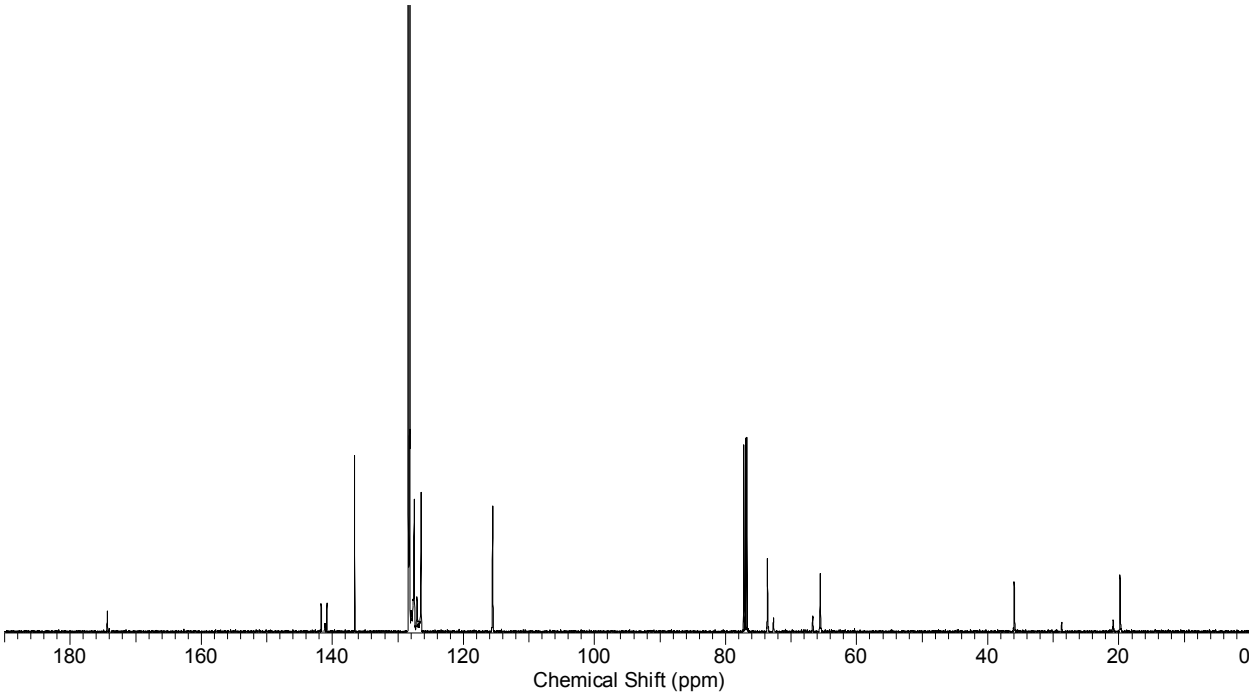
Chemical Shift (ppm)


O
N
OH
CH3
CH3
8
7
6
5
4
3
2
1
0
Chemical Shift (ppm)

85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160
140
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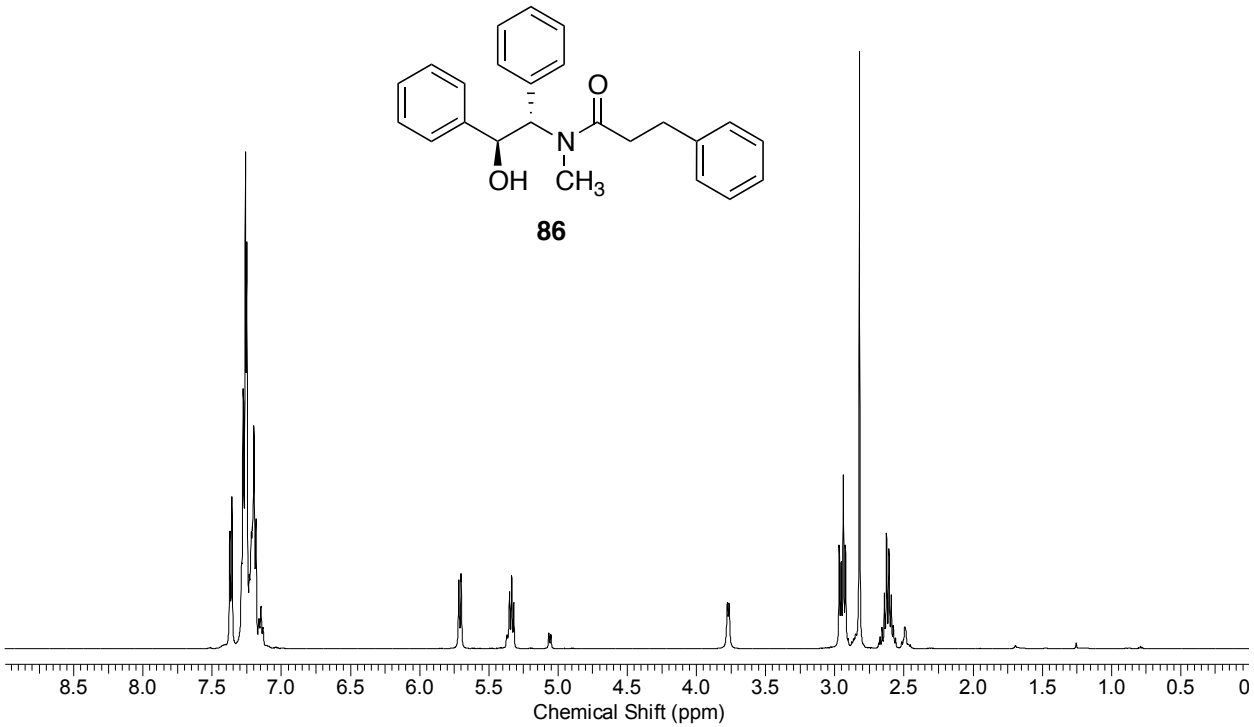
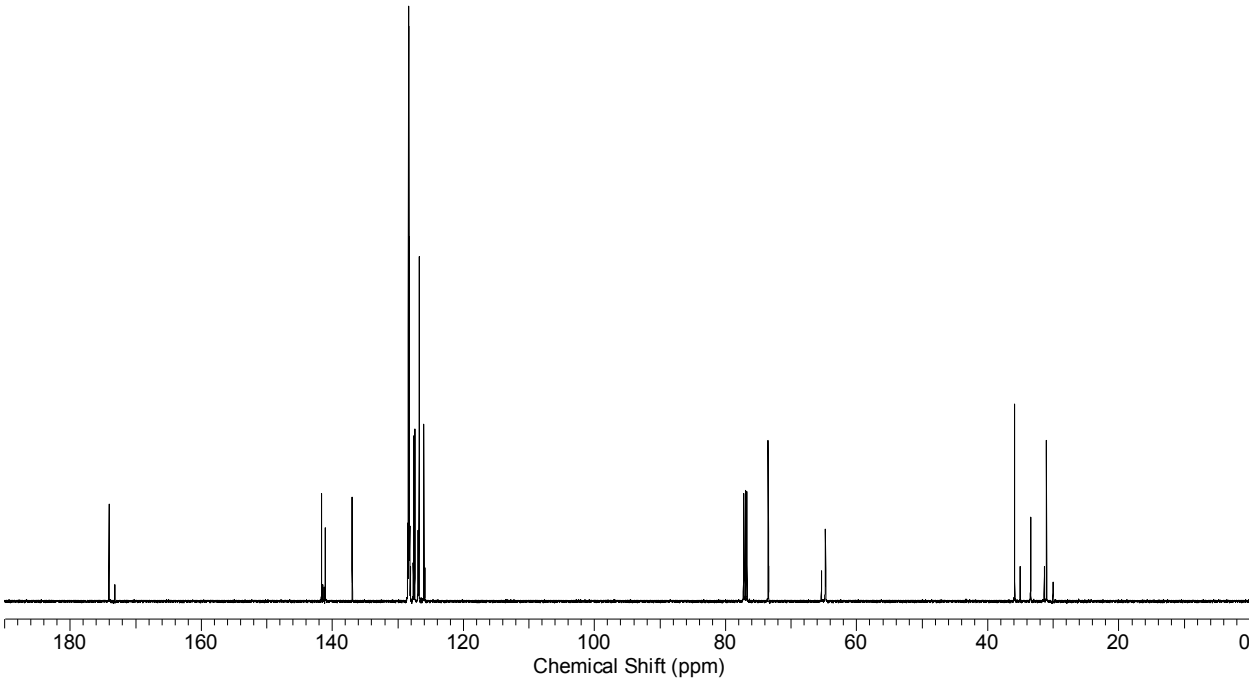
100
80
60
40
20
0
Chemical Shift (ppm)


O
N
OH
CH3
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0
Chemical Shift (ppm)

86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20
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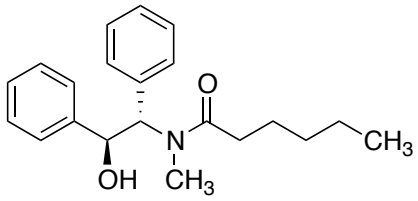
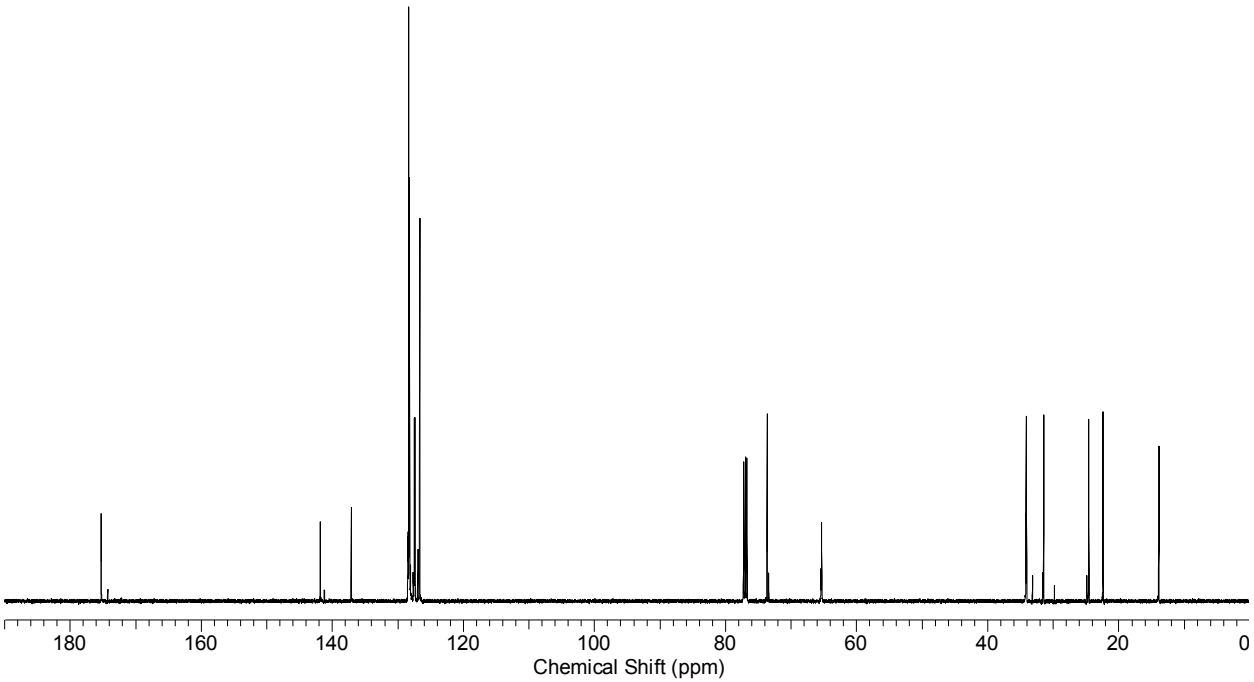
Chemical Shift (ppm)


O
N
CH3
OH
CH3

87

8
7
6
5
4
3
2
1
0
Chemical Shift (ppm)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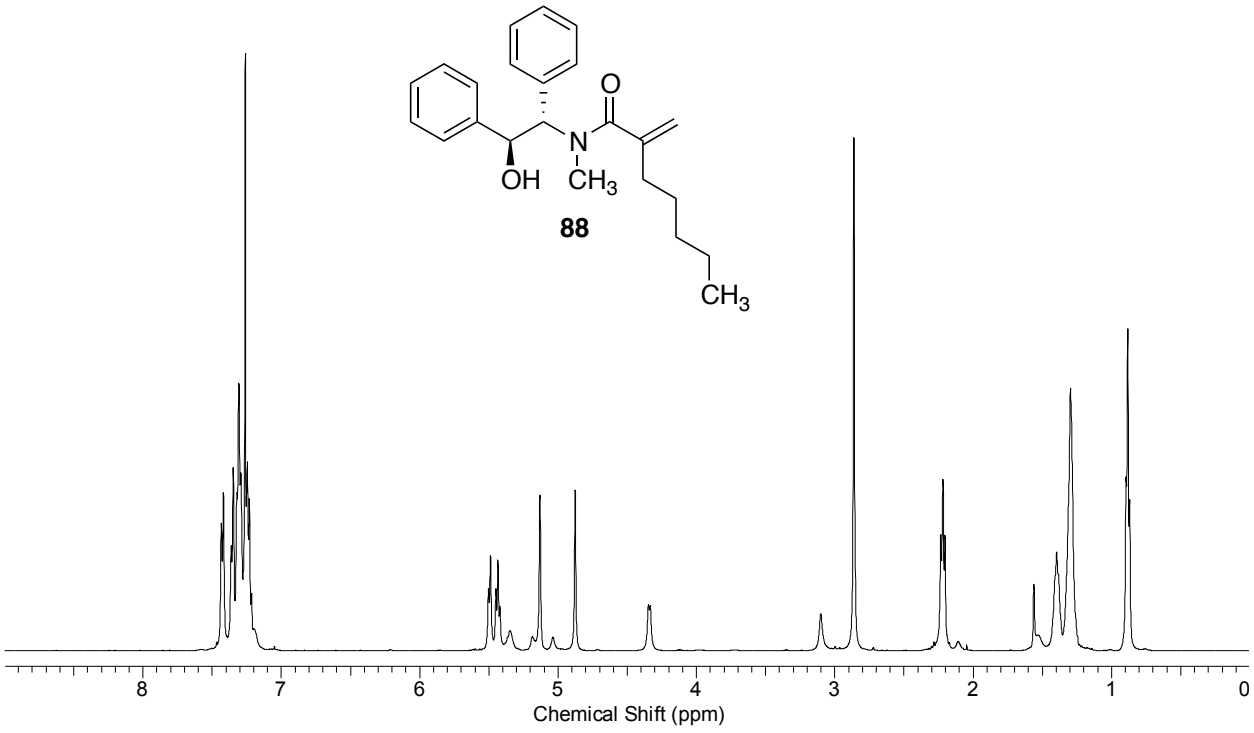
Chemical Shift (ppm)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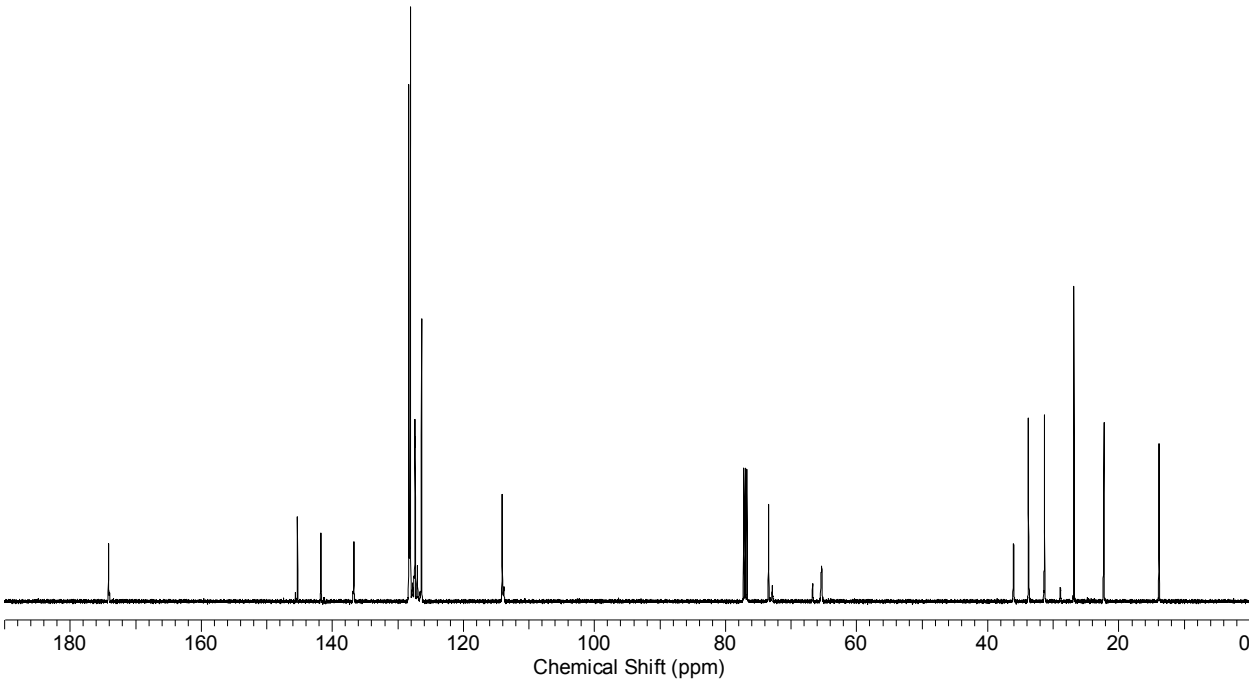
OH
CH3
CH3
88
8
7
6
5
4
3
2
1
0
Chemical Shift (ppm)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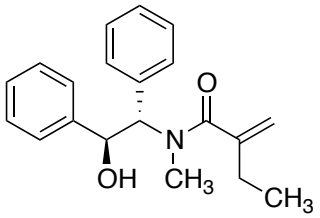
Chemical Shift (ppm)


O
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OH
CH3
CH3

89

8
7
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4
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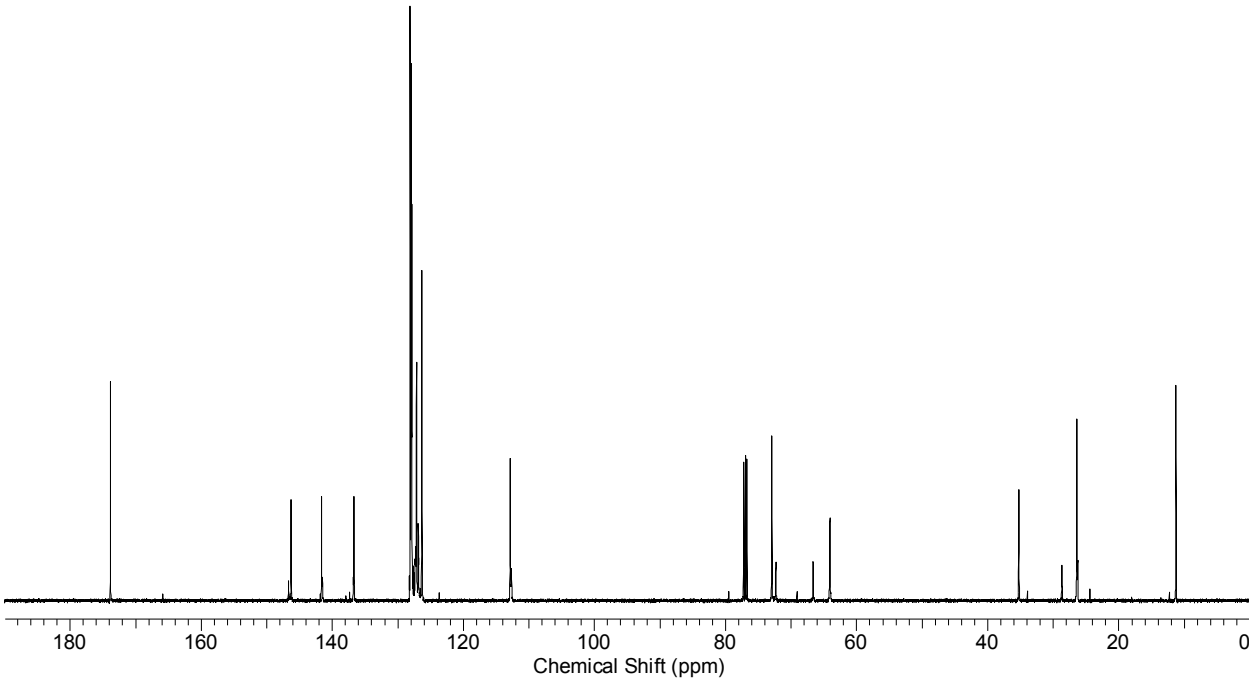
2
1
0
Chemical Shift (ppm)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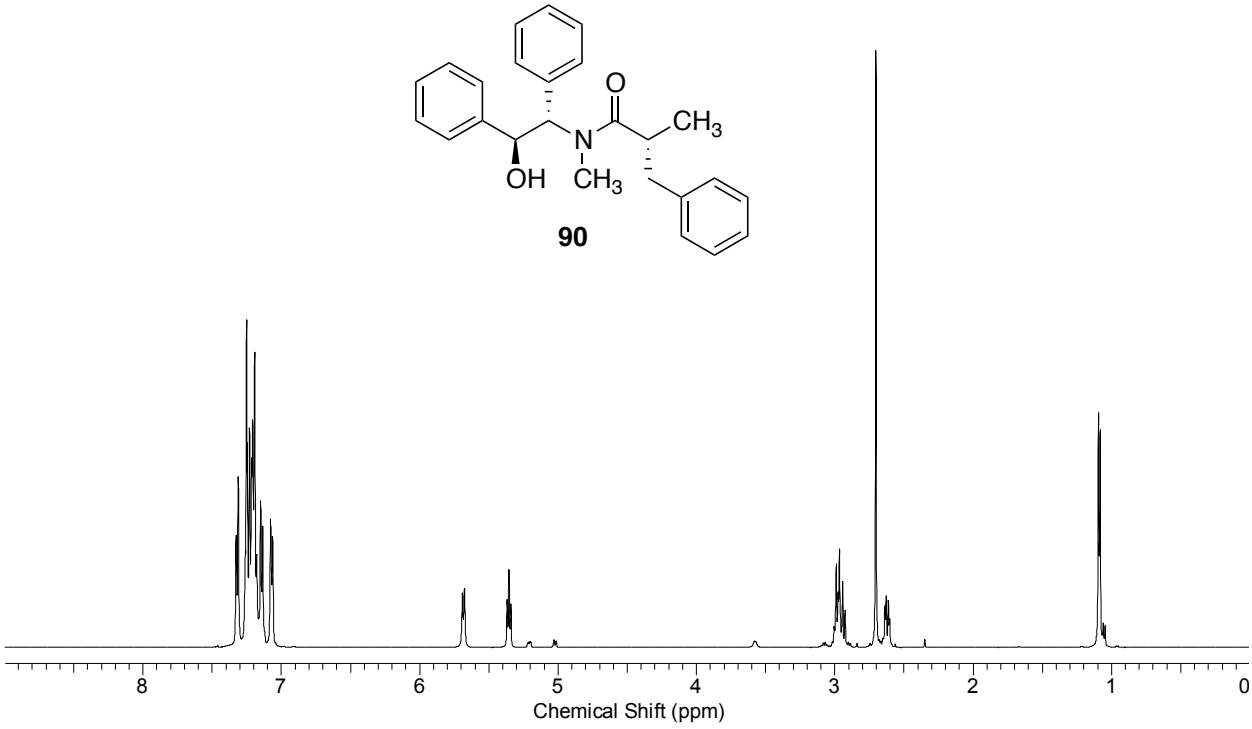
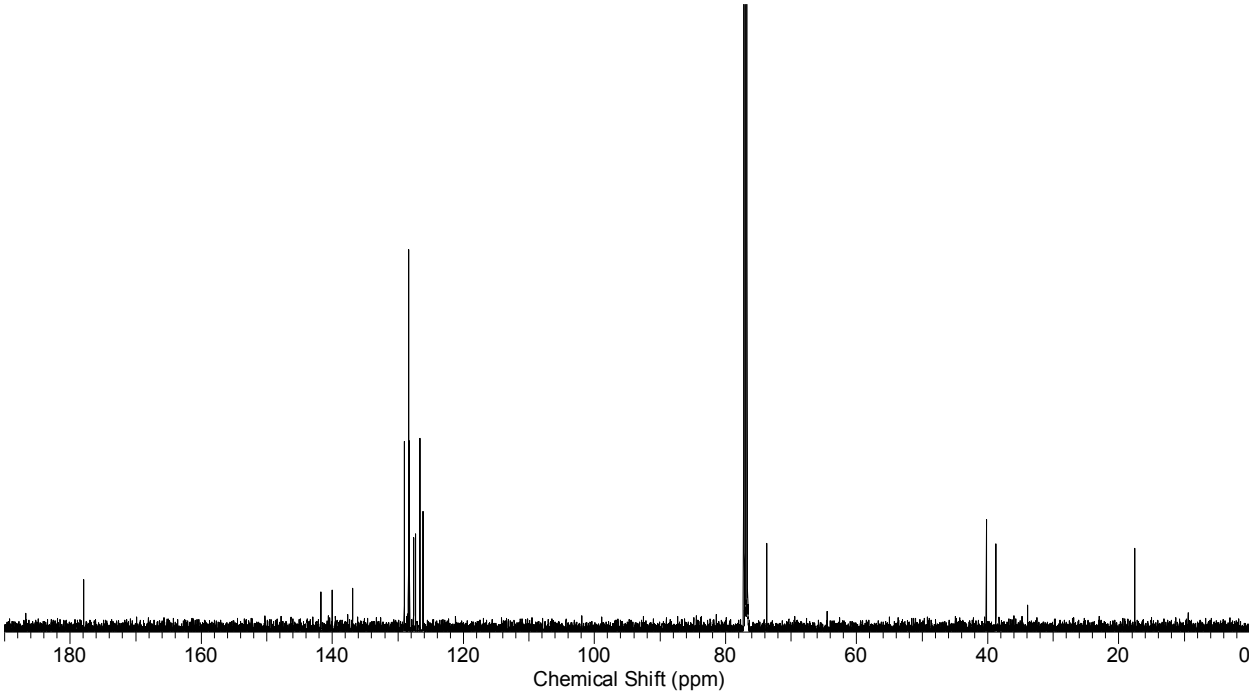
Chemical Shift (ppm)


O
CH3
N
OH
CH3
8
7
6
5
4
3
2
1
0
Chemical Shift (ppm)

90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20
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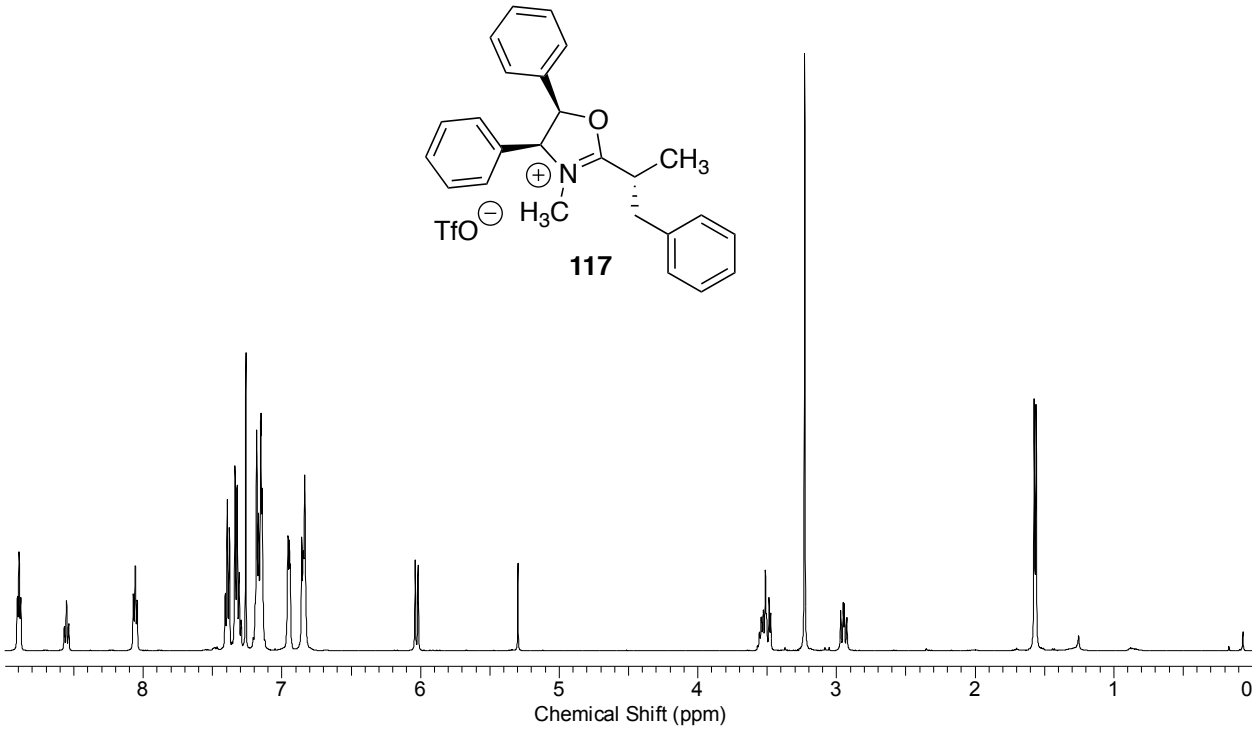
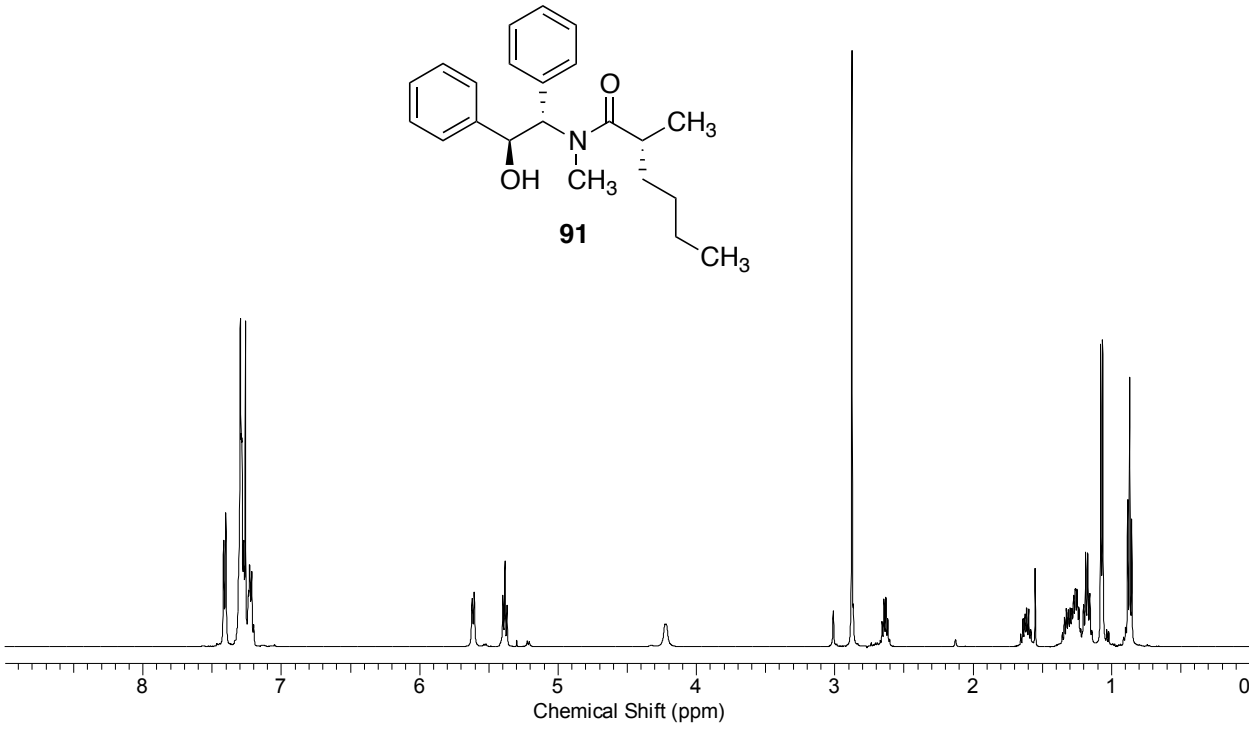
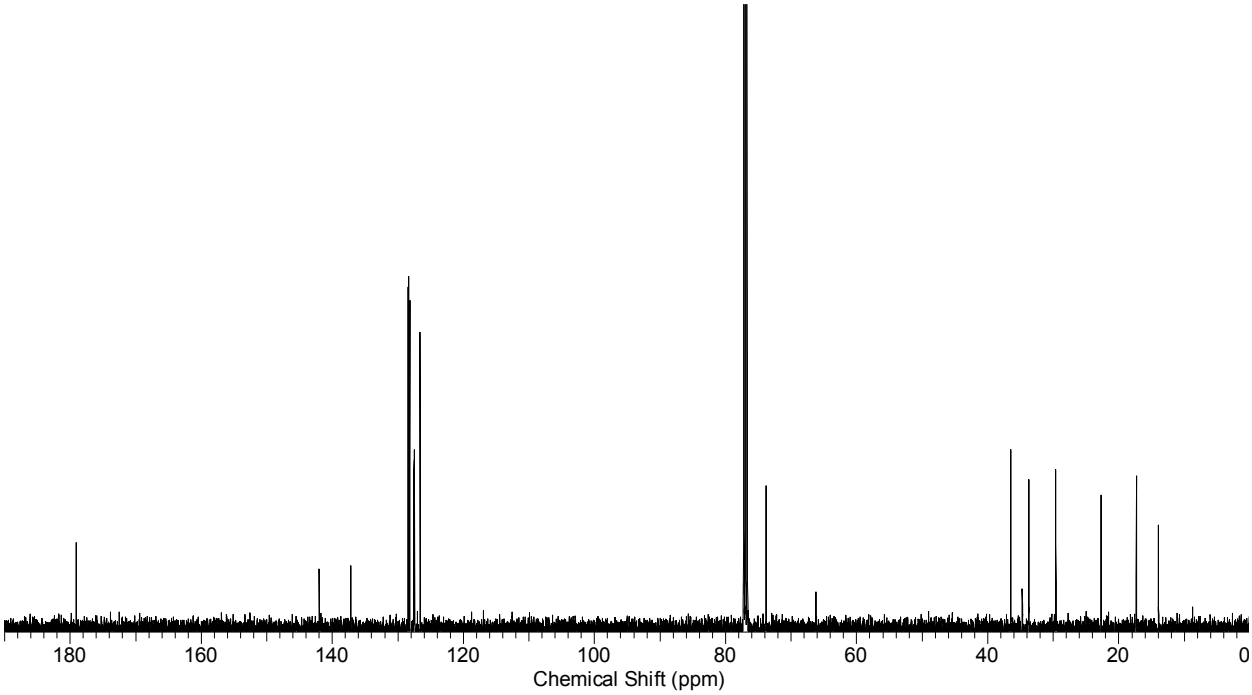
Chemical Shift (ppm)


O
CH3
N
H3C
TfO
117
8
7
6
5
4
3
2
1
0
Chemical Shift (ppm)


O
CH3
N
OH
CH3
CH3
8
7
6
5
4
3
2
1
0
Chemical Shift (ppm)

91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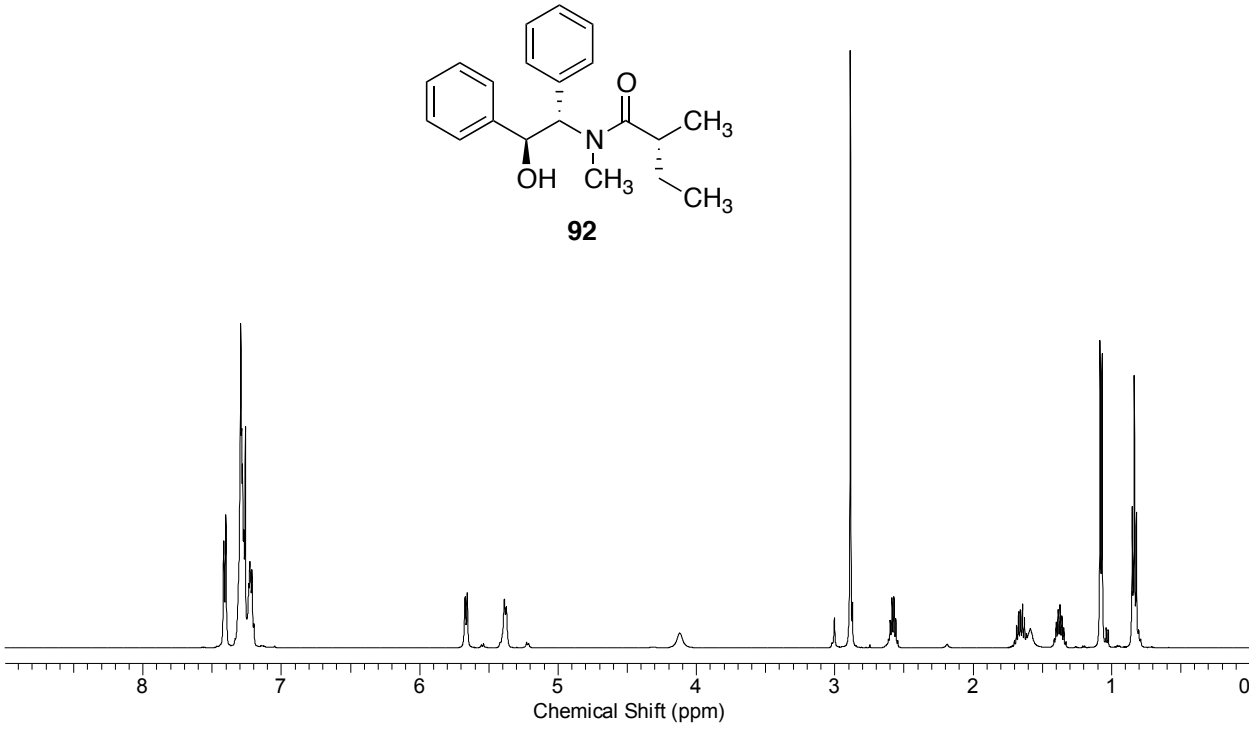
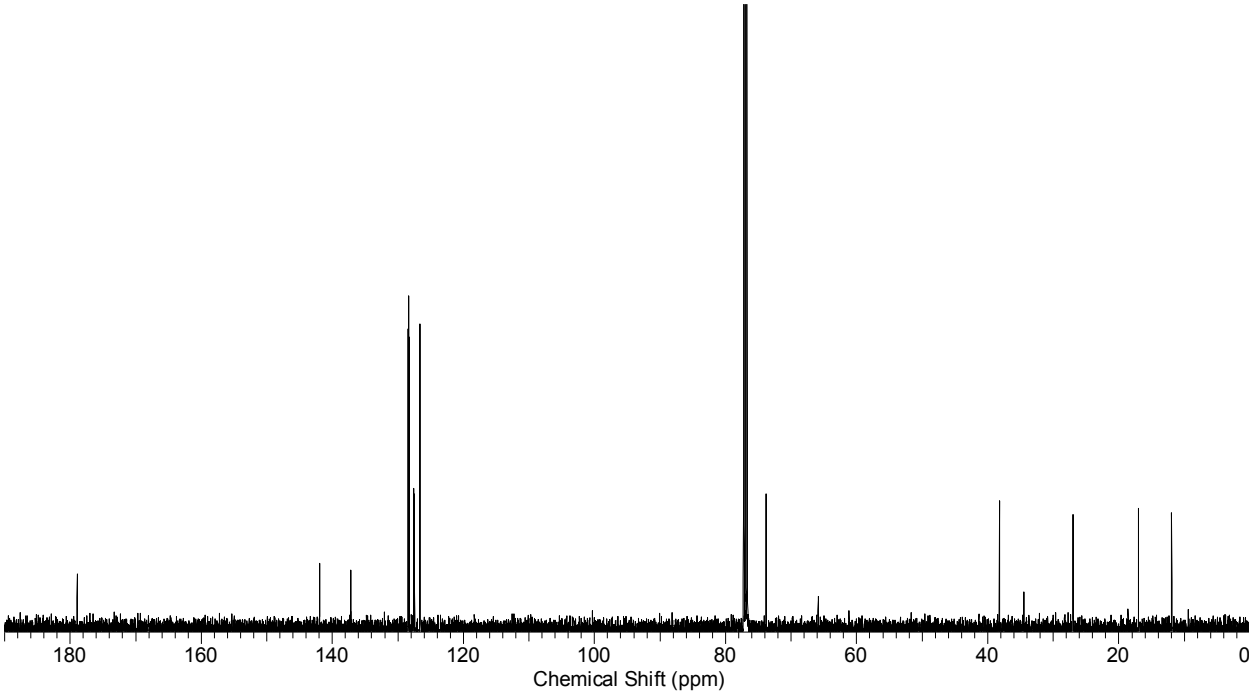
100
80
60
40
20
0
Chemical Shift (ppm)


O
CH3
N
OH
CH3
CH3
8
7
6
5
4
3
2
1
0
Chemical Shift (ppm)

92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100
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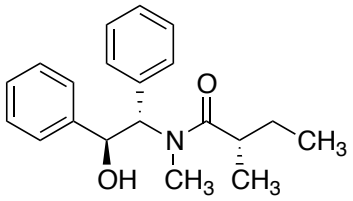
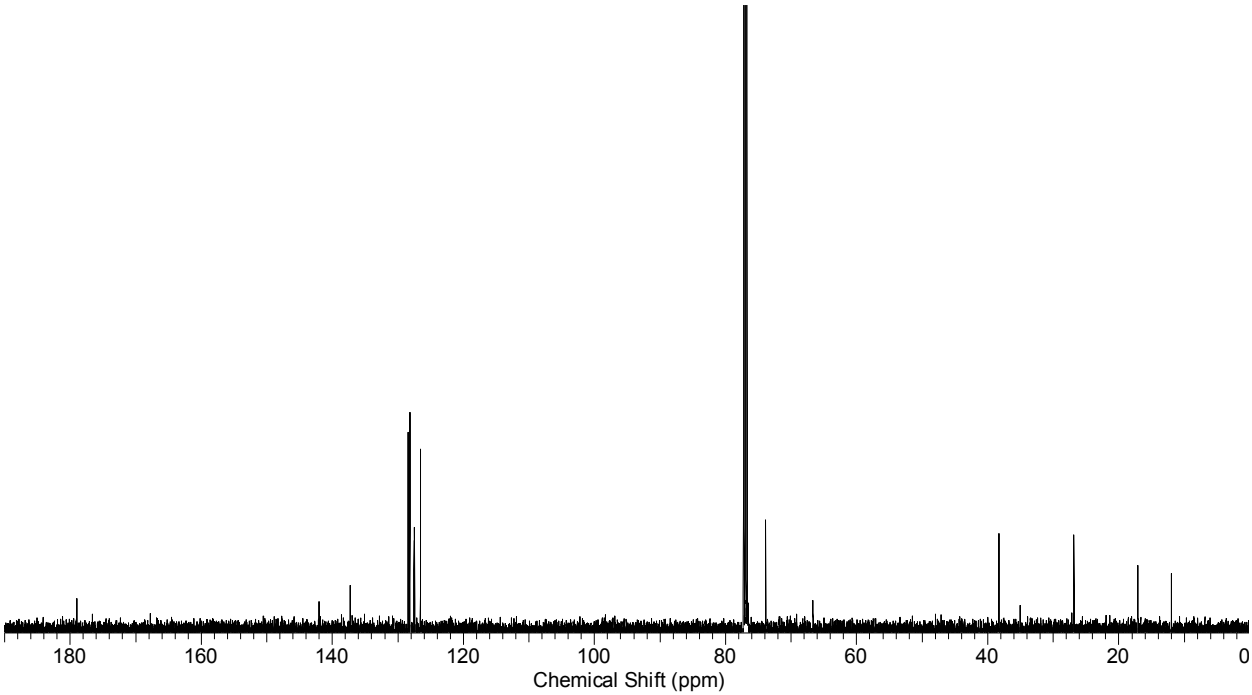
20
0
Chemical Shift (ppm)


O
N
CH3
OH
CH3
CH3

93

8
7
6
5
4
3
2
1
0
Chemical Shift (ppm)


180
160
140
120
100
80
60
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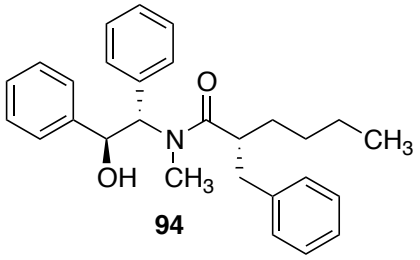
20
0
Chemical Shift (ppm)


O
N
CH3
OH
CH3

94

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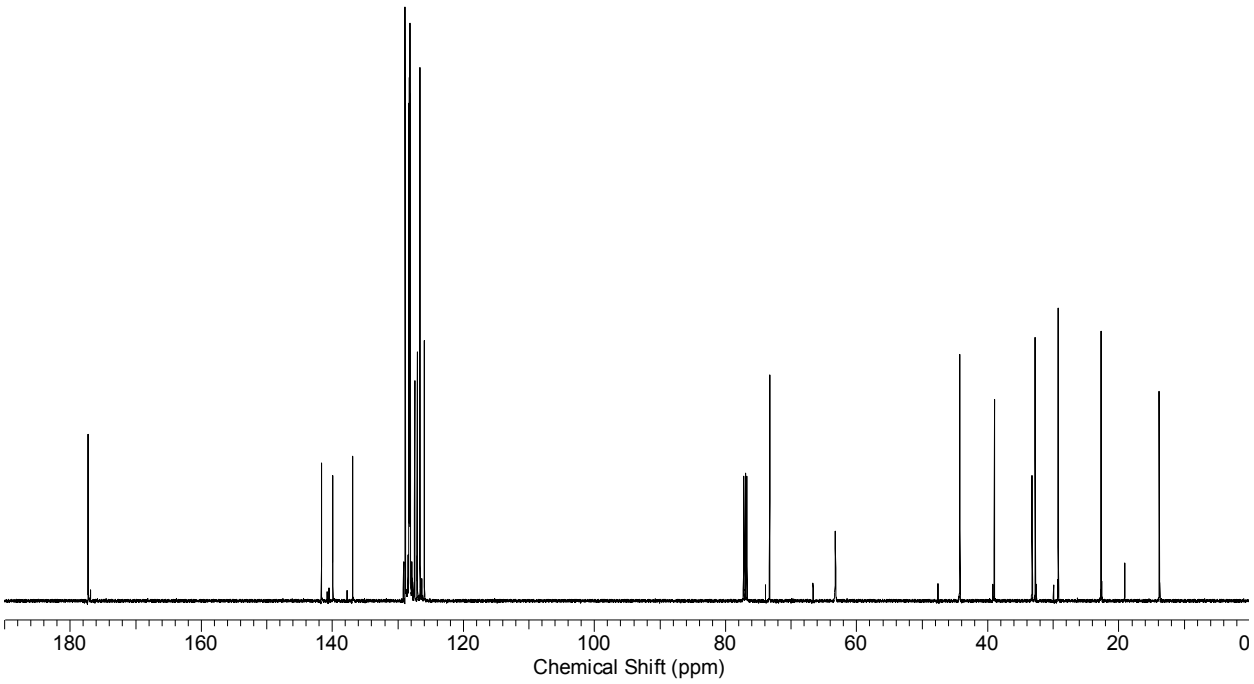
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0
Chemical Shift (ppm)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100
80
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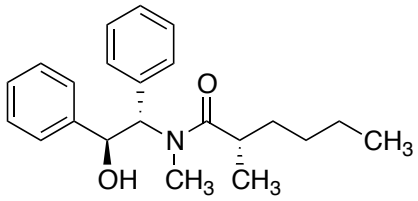
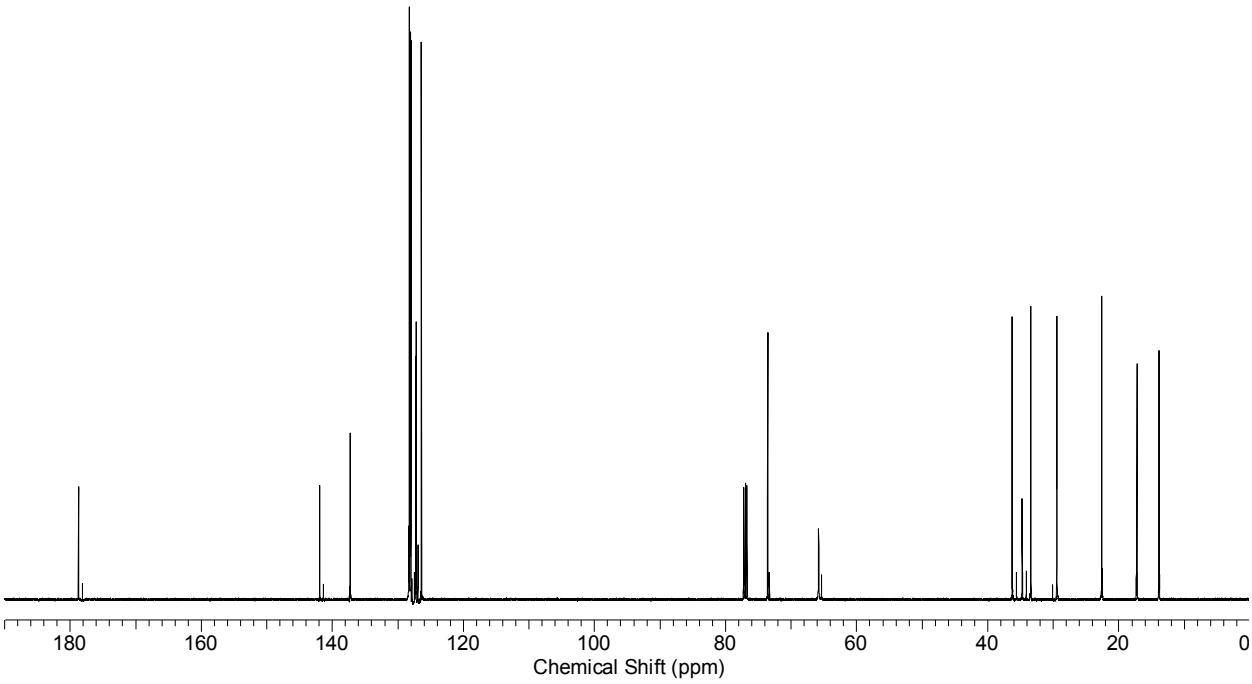
Chemical Shift (ppm)


O
N
CH3
OH
CH3
CH3

95

8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0
Chemical Shift (ppm)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100
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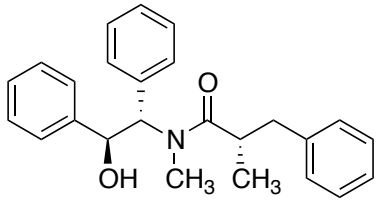
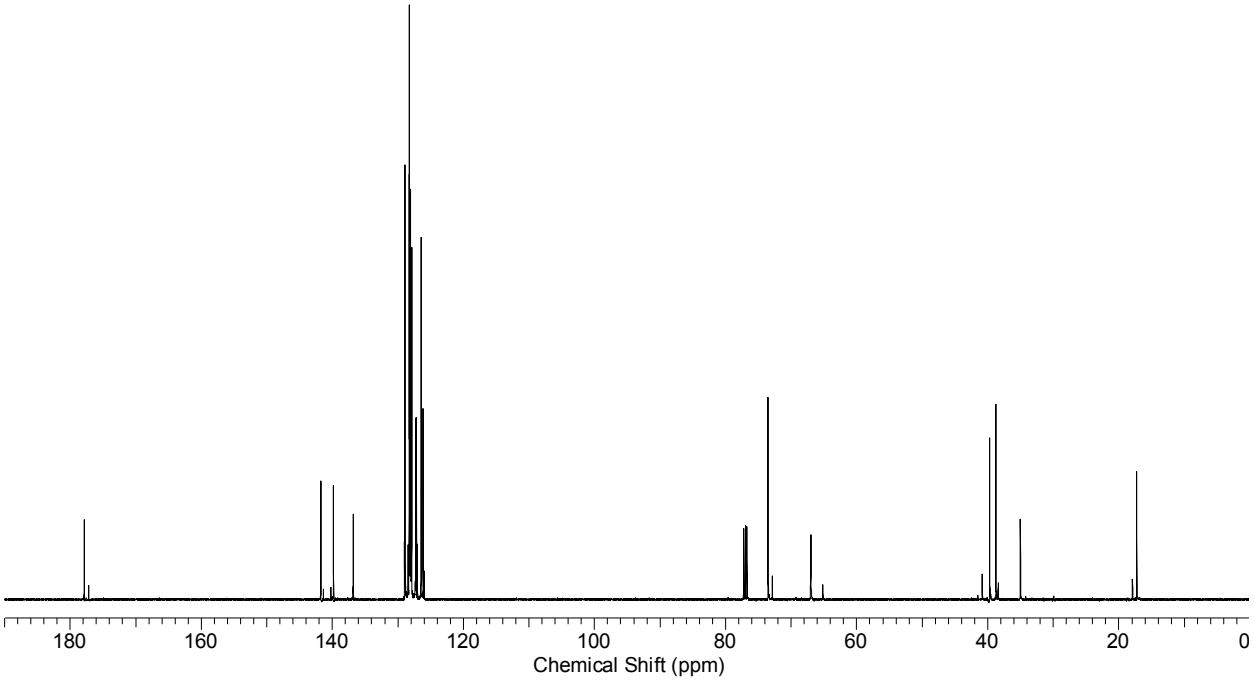
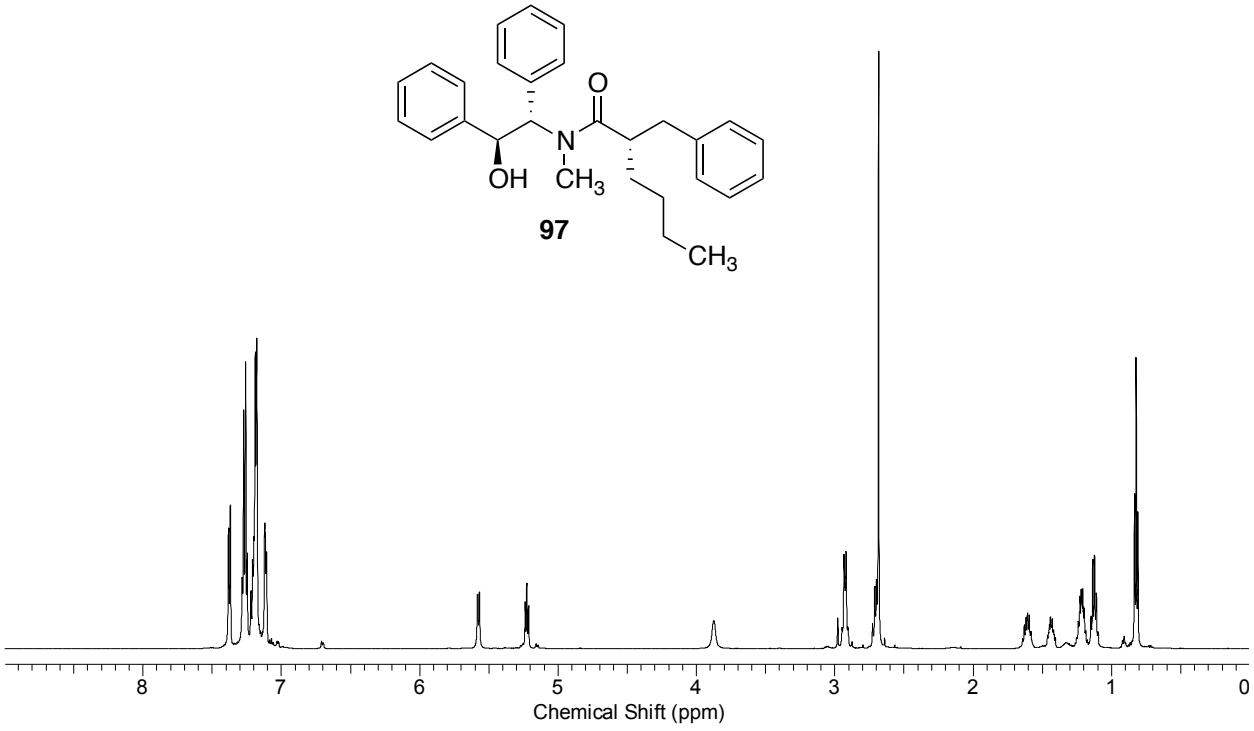
Chemical Shift (ppm)

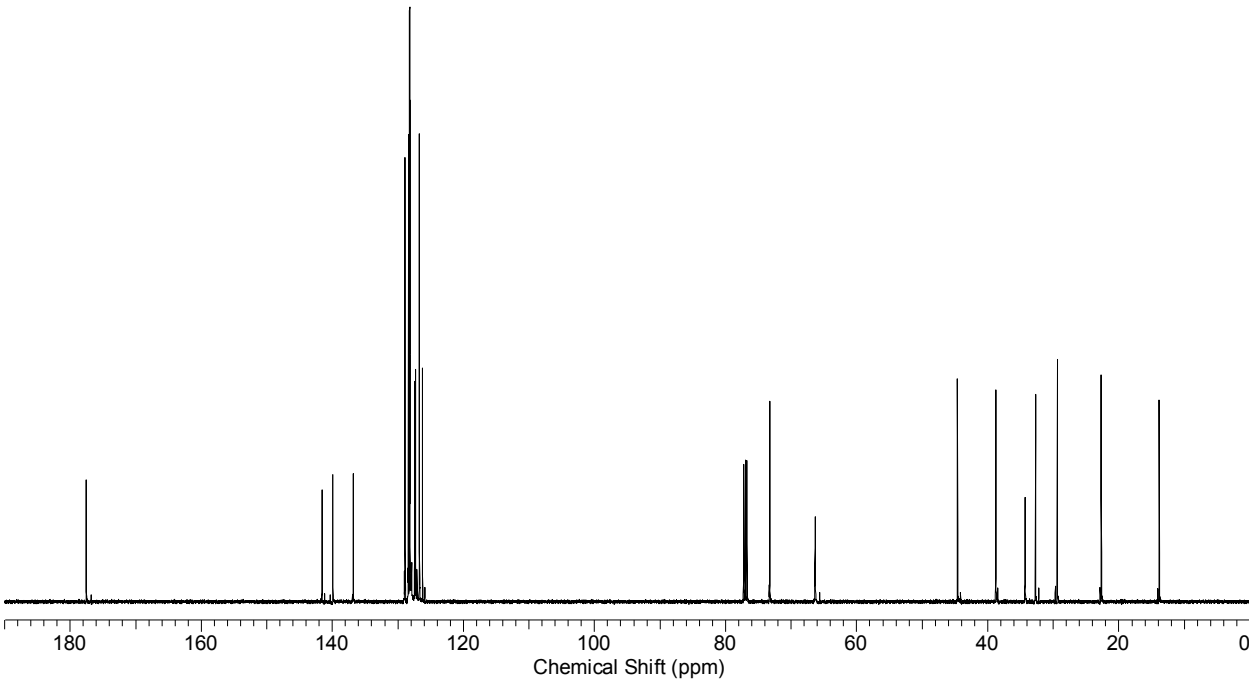

O
N
OH
CH3
CH3

96

8
7
6
5
4
3
2
1
0
Chemical Shift (ppm)


180
160
140
120
100
80
60
40
20
0
Chemical Shift (ppm)


O
N
OH
CH3
CH3
97
8
7
6
5
4
3
2
1
0
Chemical Shift (ppm)


180
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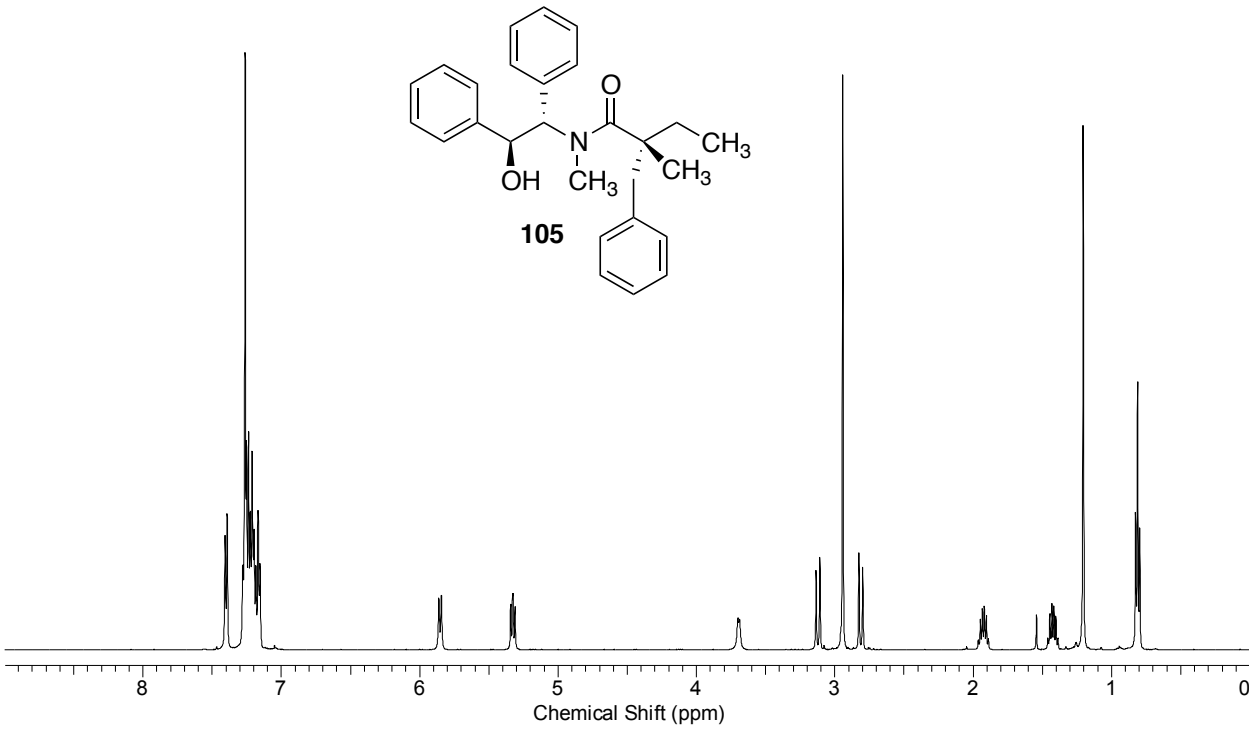
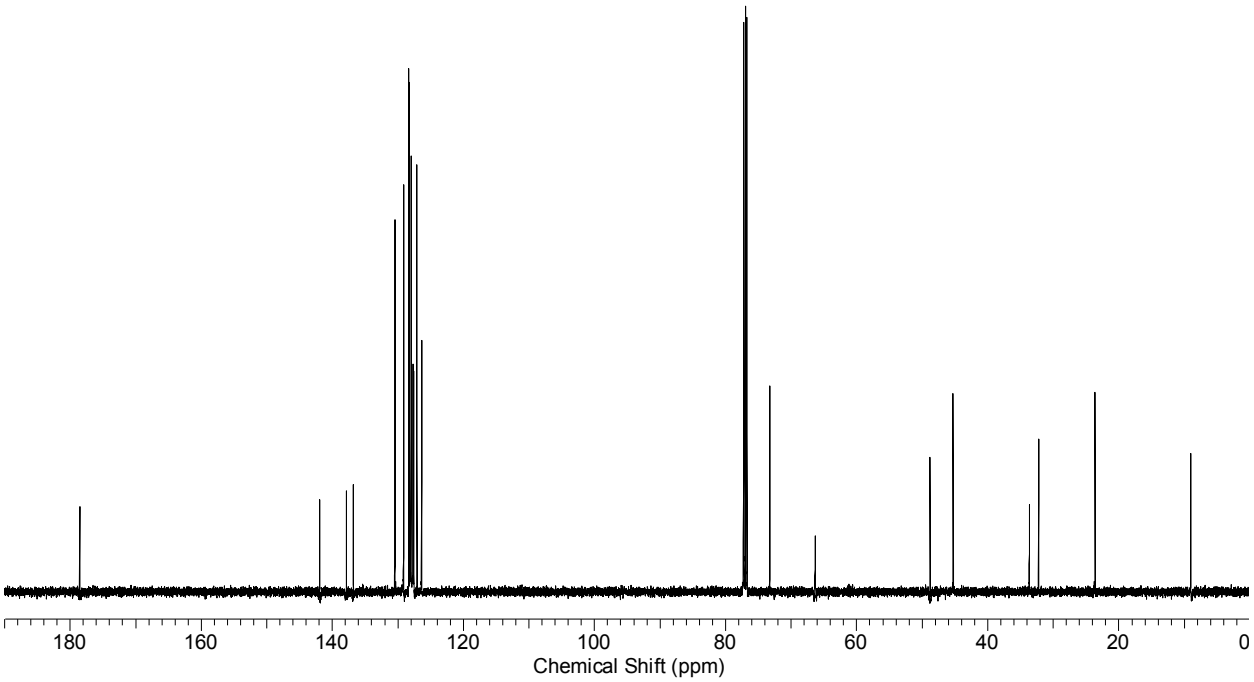
100
80
60
40
20
0
Chemical Shift (ppm)


O
N
CH3
CH3
OH
CH3
105
8
7
6
5
4
3
2
1
0
Chemical Shift (ppm)


180
160
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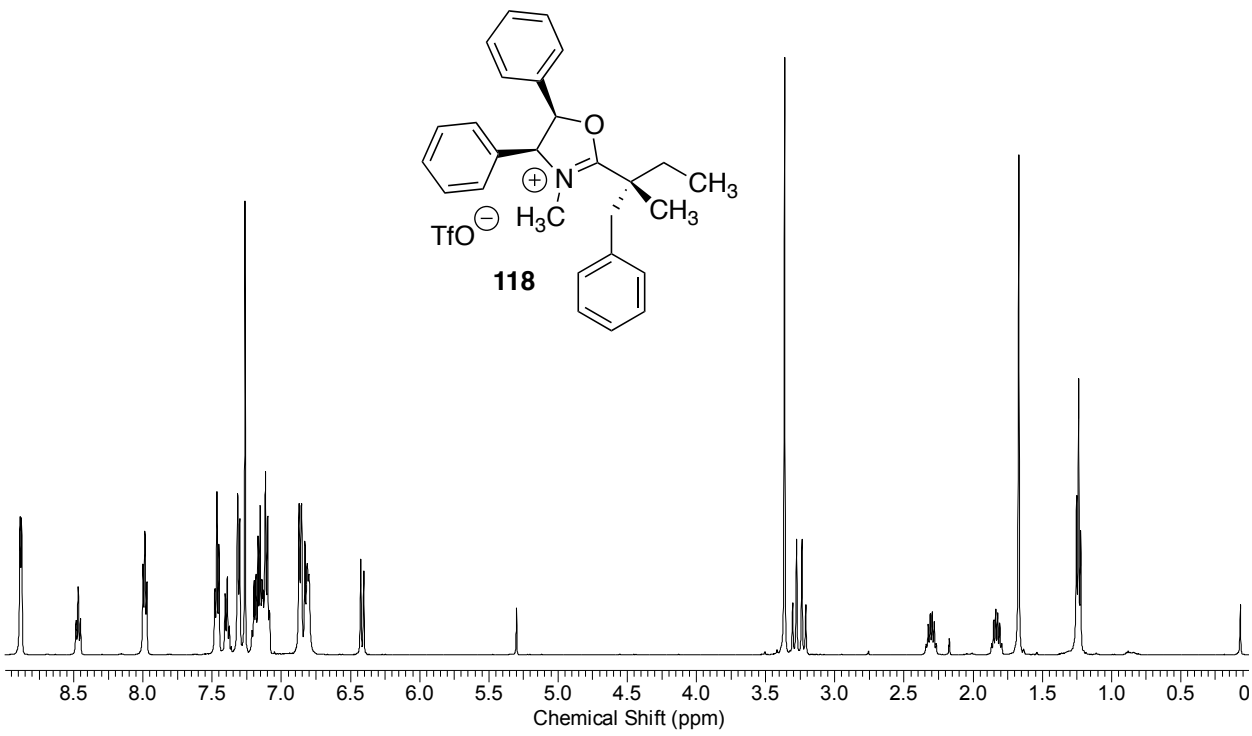
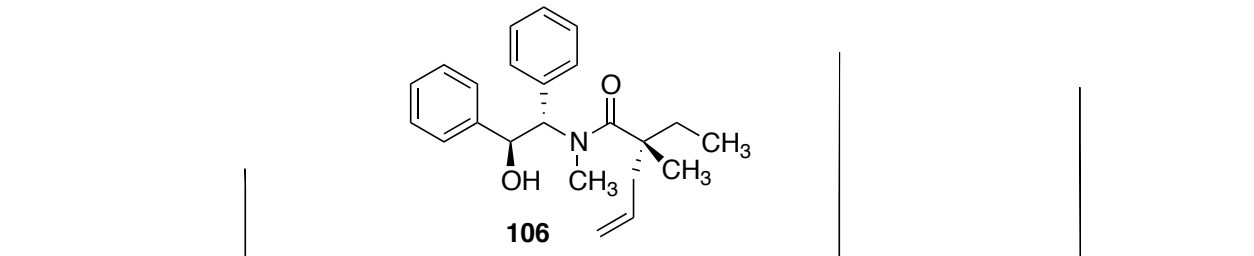
100
80
60
40
20
0
Chemical Shift (ppm)

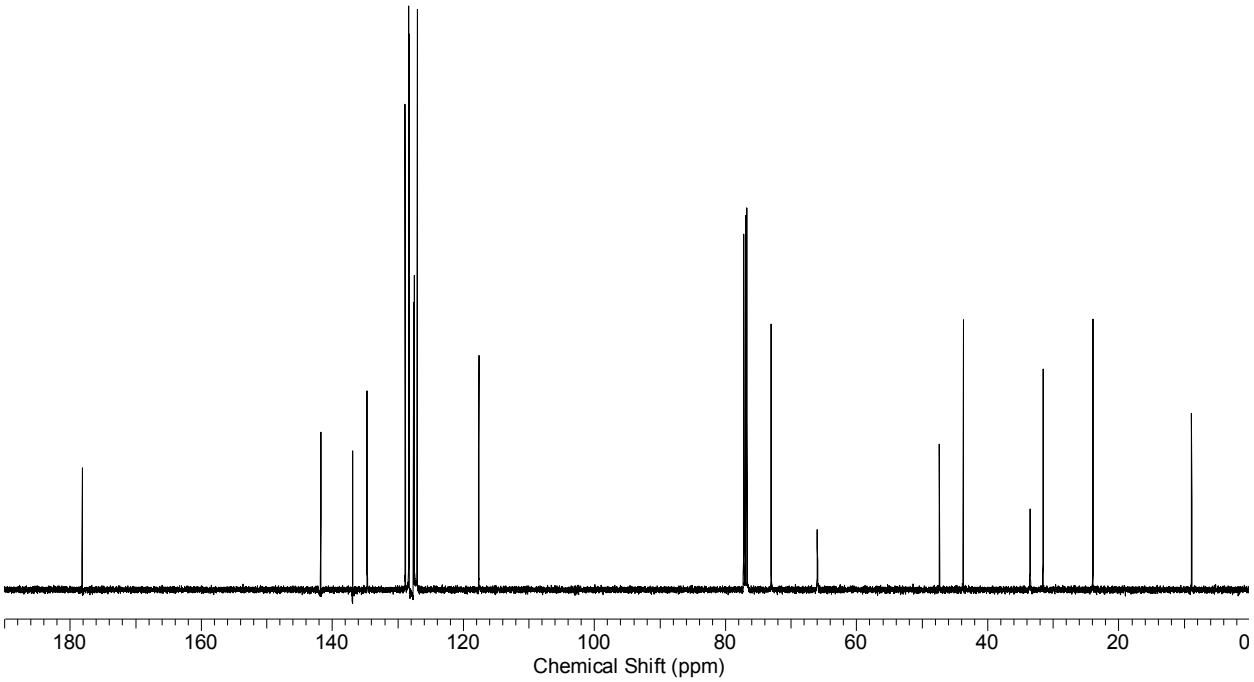

O
N
CH3
CH3
H3C
TfO
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0
Chemical Shift (ppm)

118


O
N
CH3
CH3
OH
CH3

106

8
7
6
5
4
3
2
1
0
Chemical Shift (ppm)


180
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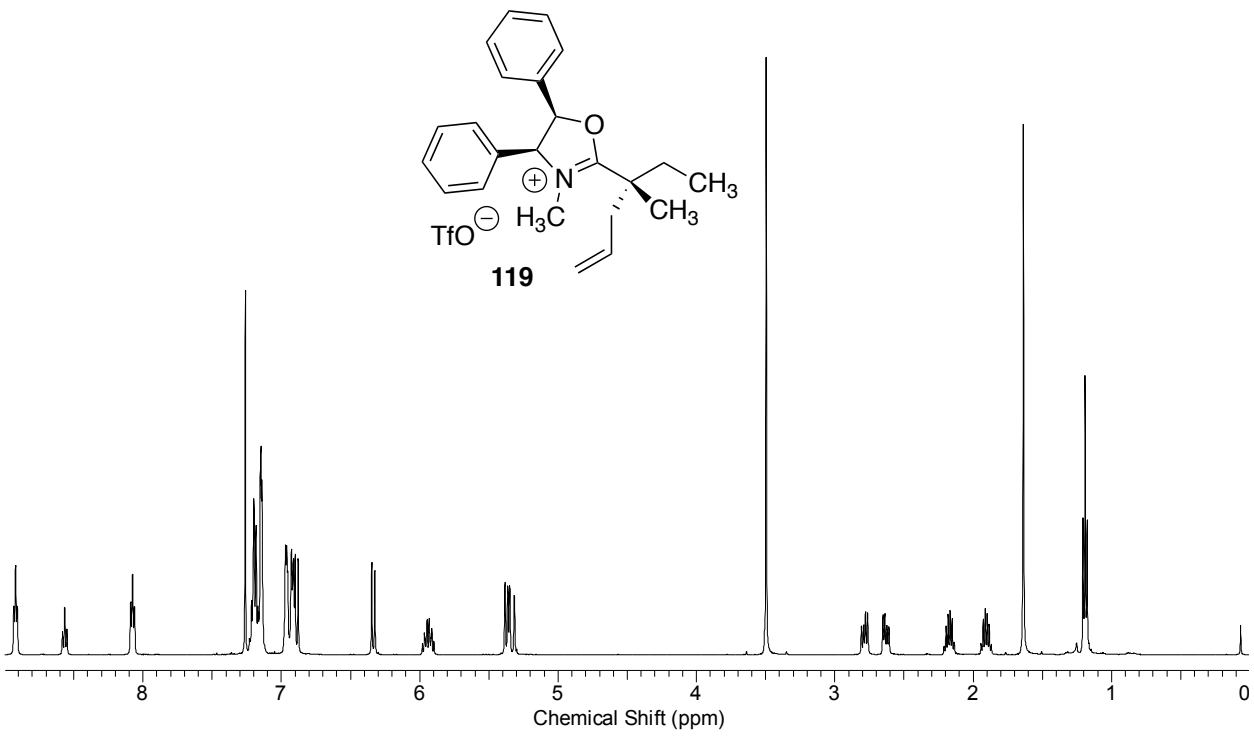
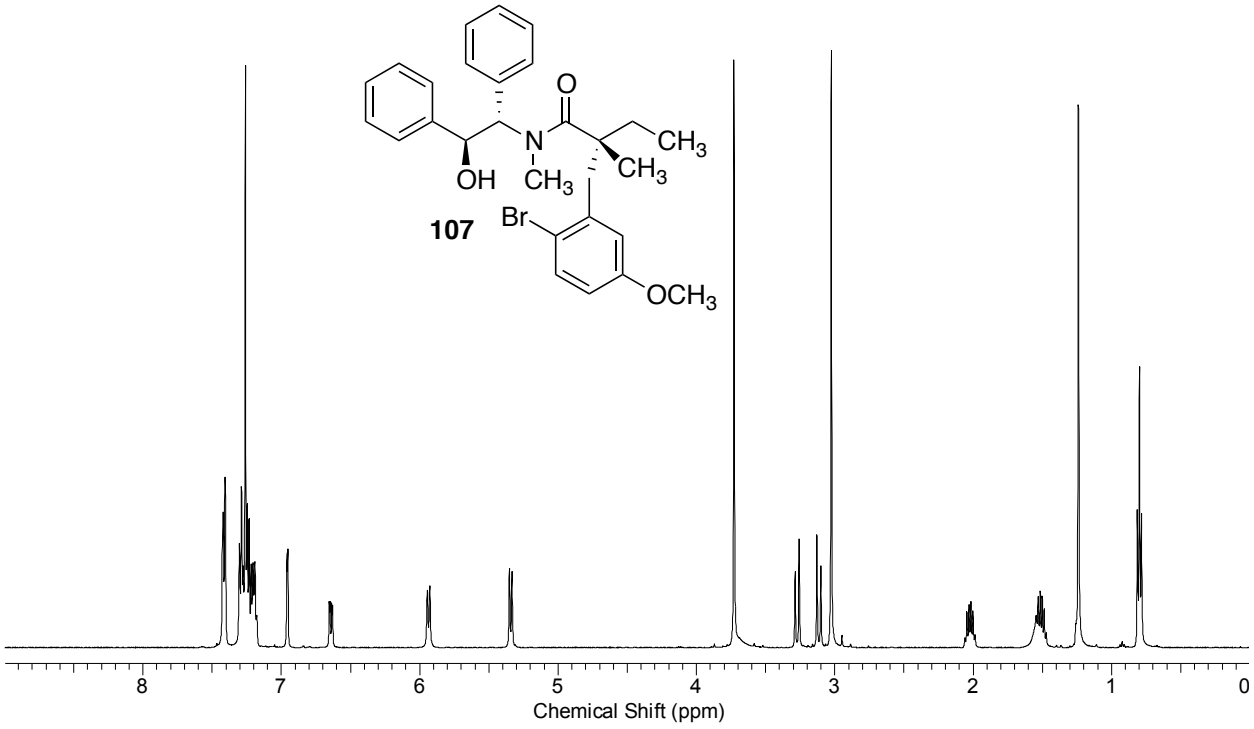
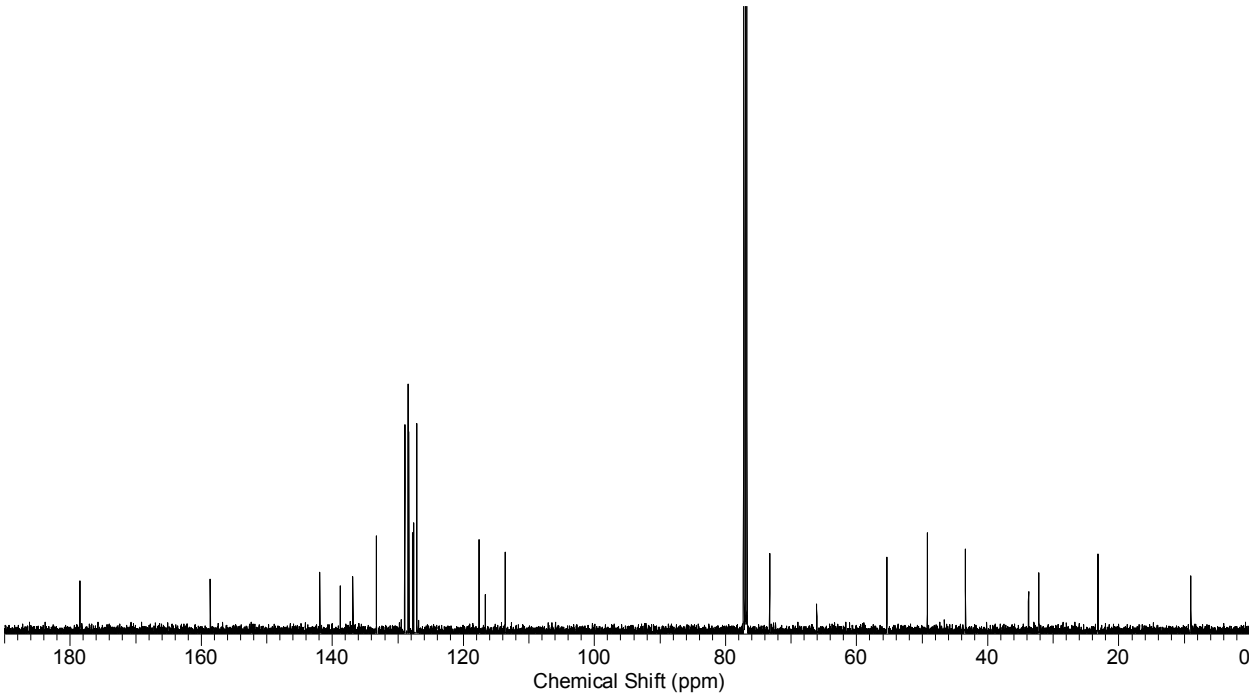
140
120
100
80
60
40
20
0
Chemical Shift (ppm)



119


O
N
CH3
CH3
CH3
OH
CH3
Br
OCH3
107
8
7
6
5
4
3
2
1
0
Chemical Shift (ppm)


180
160
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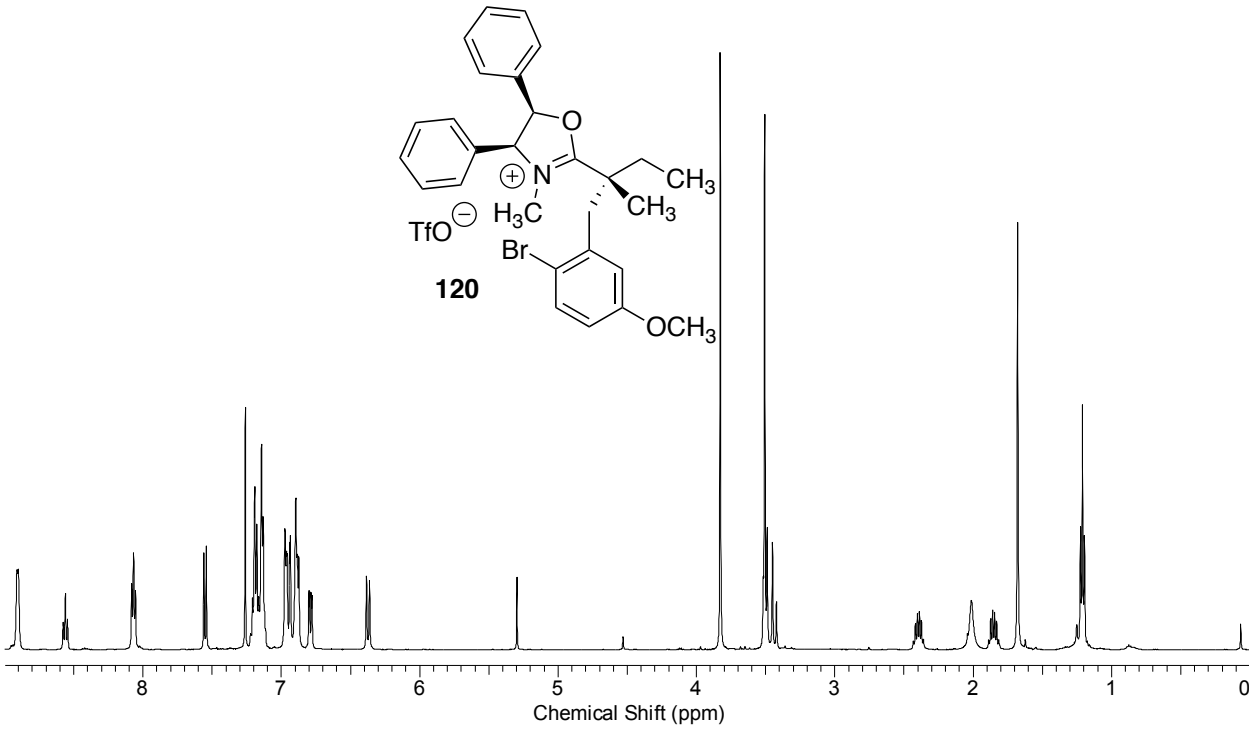
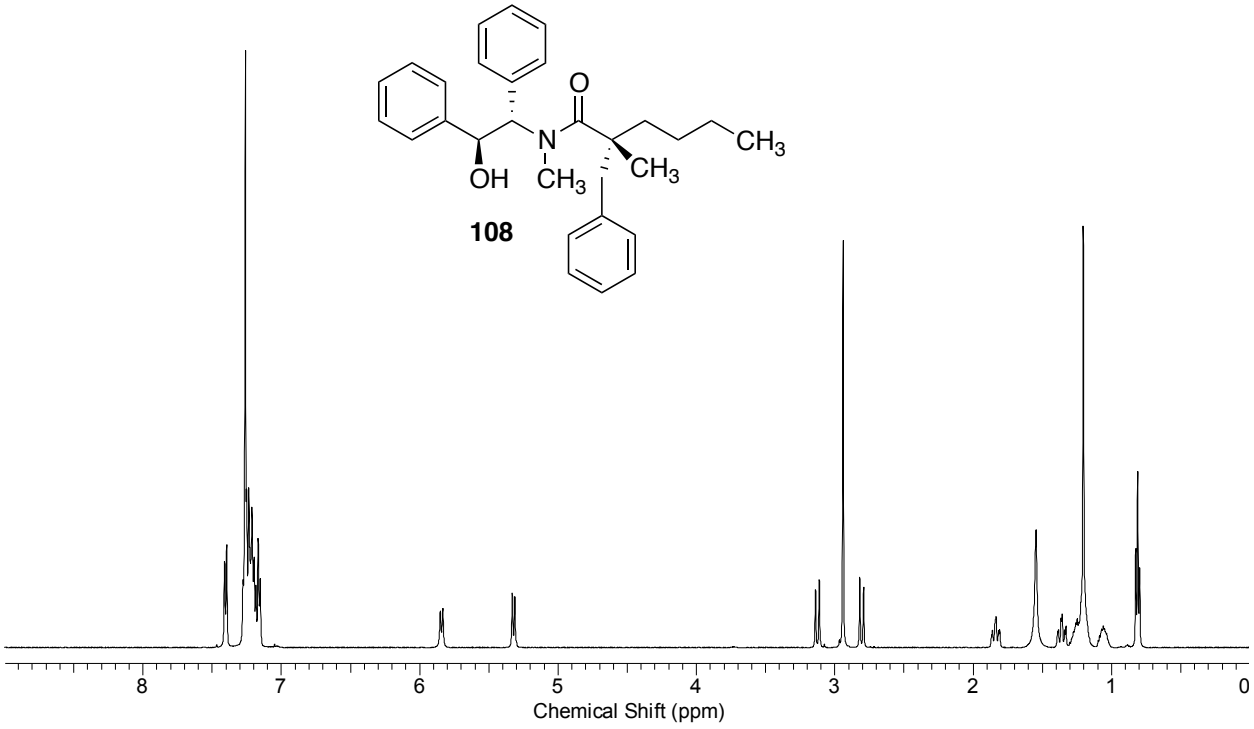
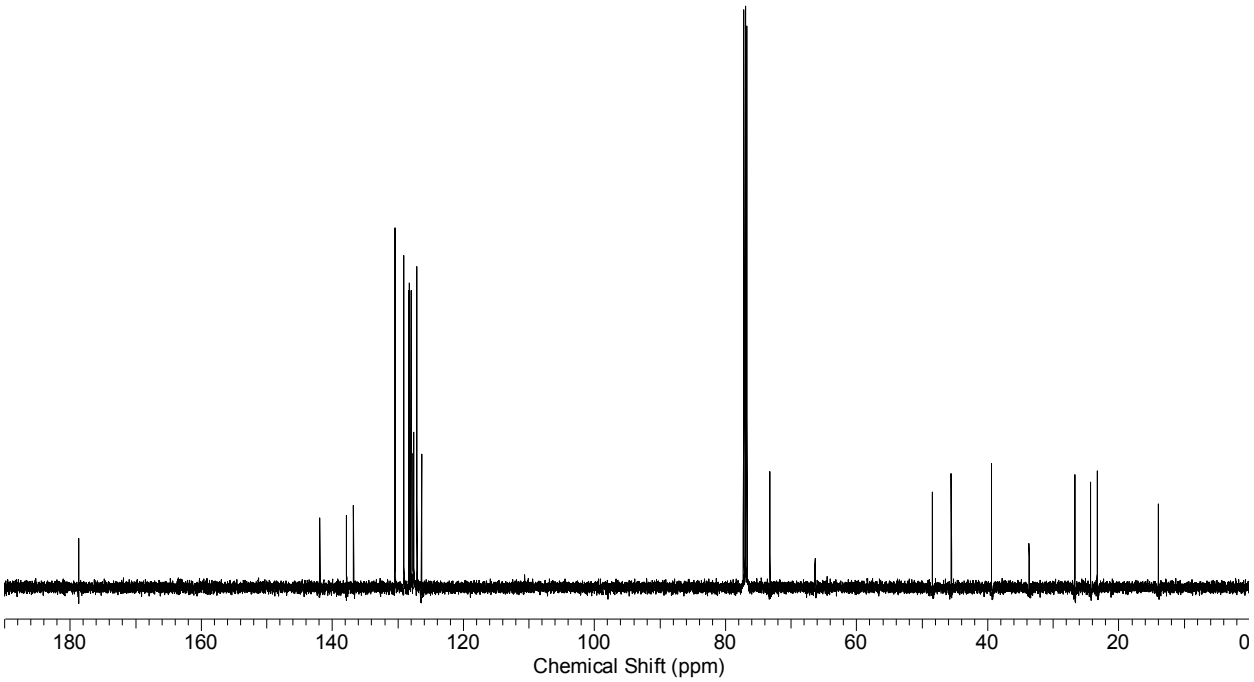
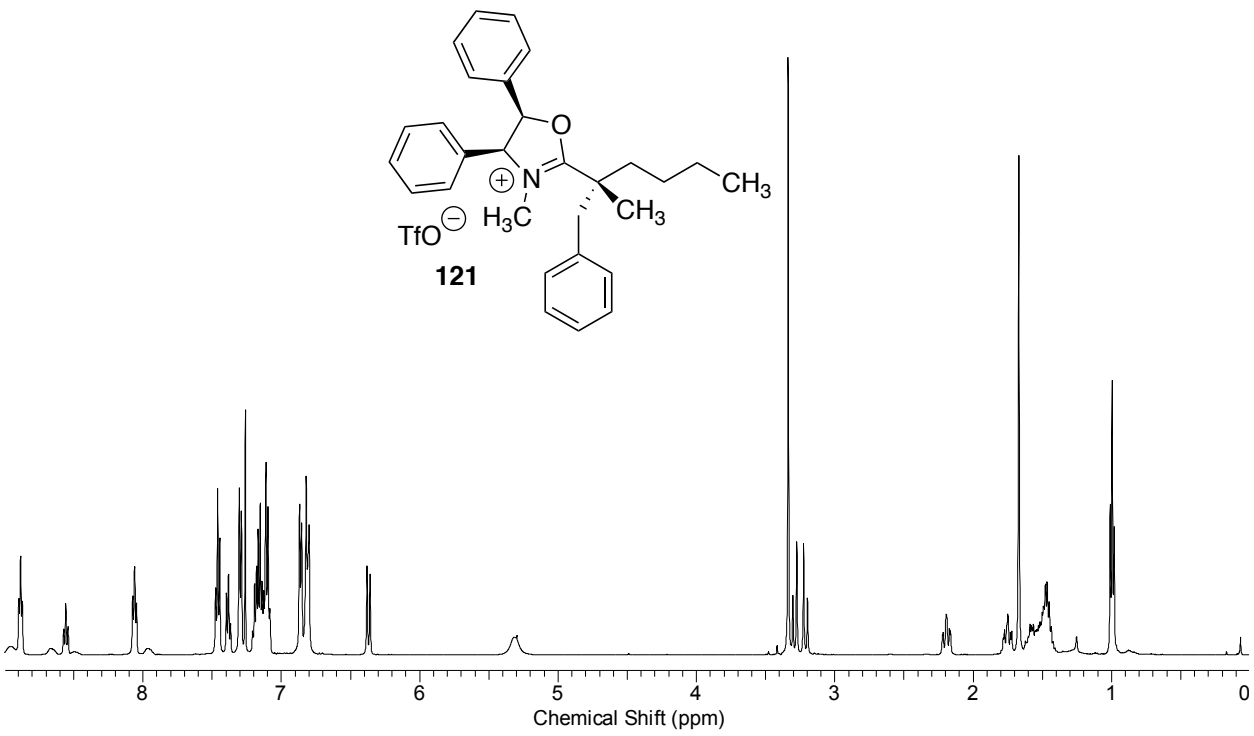
120
100
80
60
40
20
0
Chemical Shift (ppm)

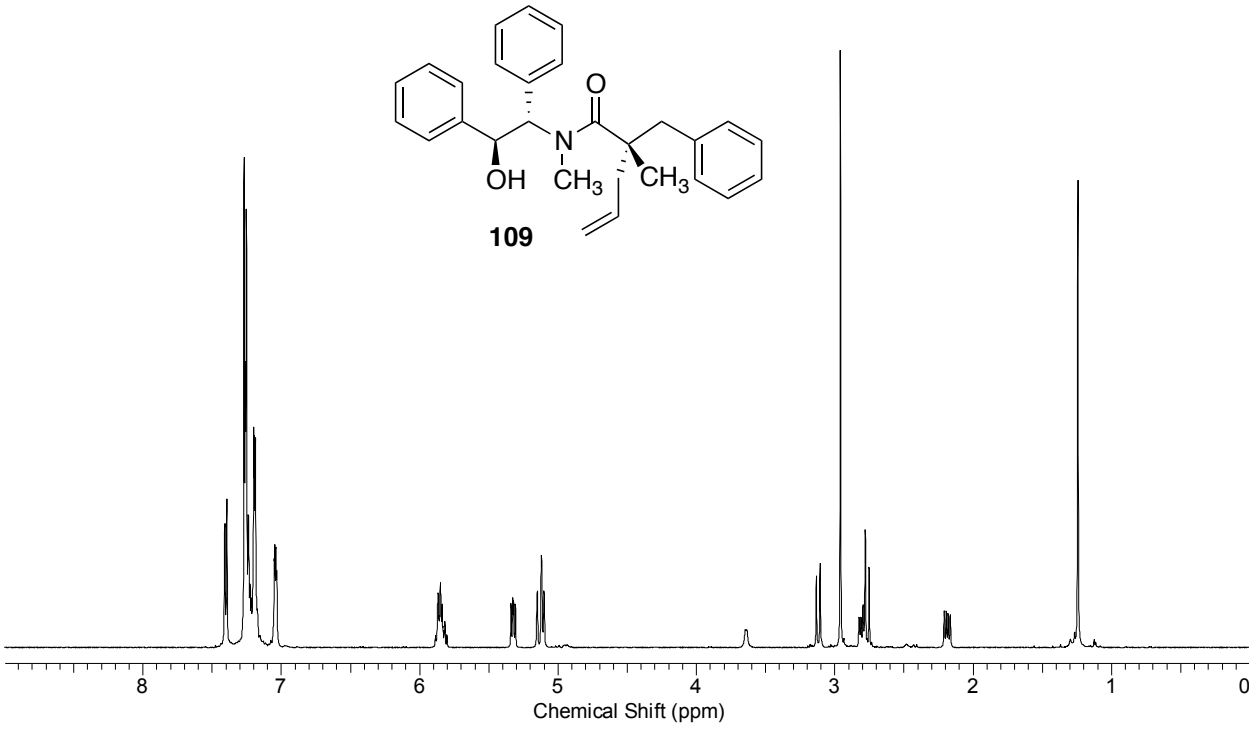

O
N
CH3
CH3
H3C
TfO
Br
OCH3
120
8
7
6
5
4
3
2
1
0
Chemical Shift (ppm)


O
N
CH3
CH3
CH3
OH
8
7
6
5
4
3
2
1
0
Chemical Shift (ppm)

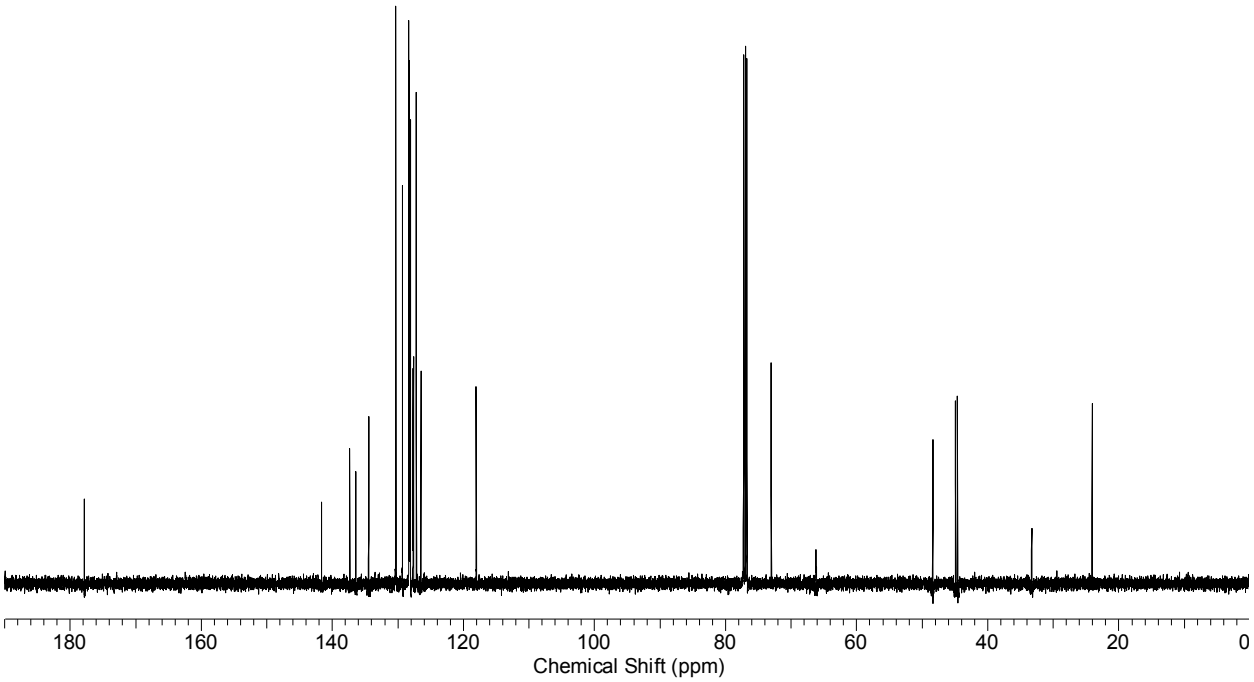
108

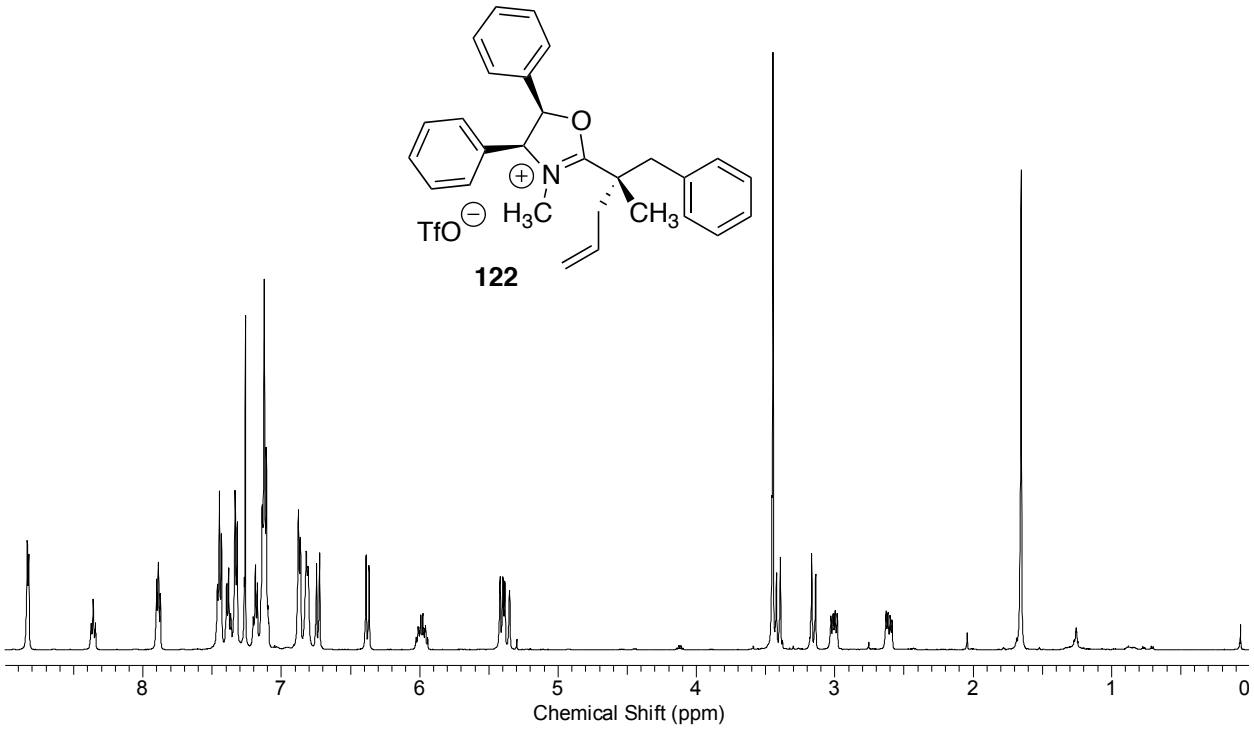

180
160
140
120
100
80
60
40
20
0
Chemical Shift (ppm)


O
N
CH3
H3C
CH3
TfO
121
8
7
6
5
4
3
2
1
0
Chemical Shift (ppm)

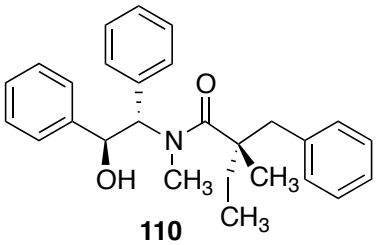

O
N
OH
CH3
CH3
8
7
6
5
4
3
2
1
0
Chemical Shift (ppm)

109


180
160
140
120
100
80
60
40
20
0
Chemical Shift (ppm)



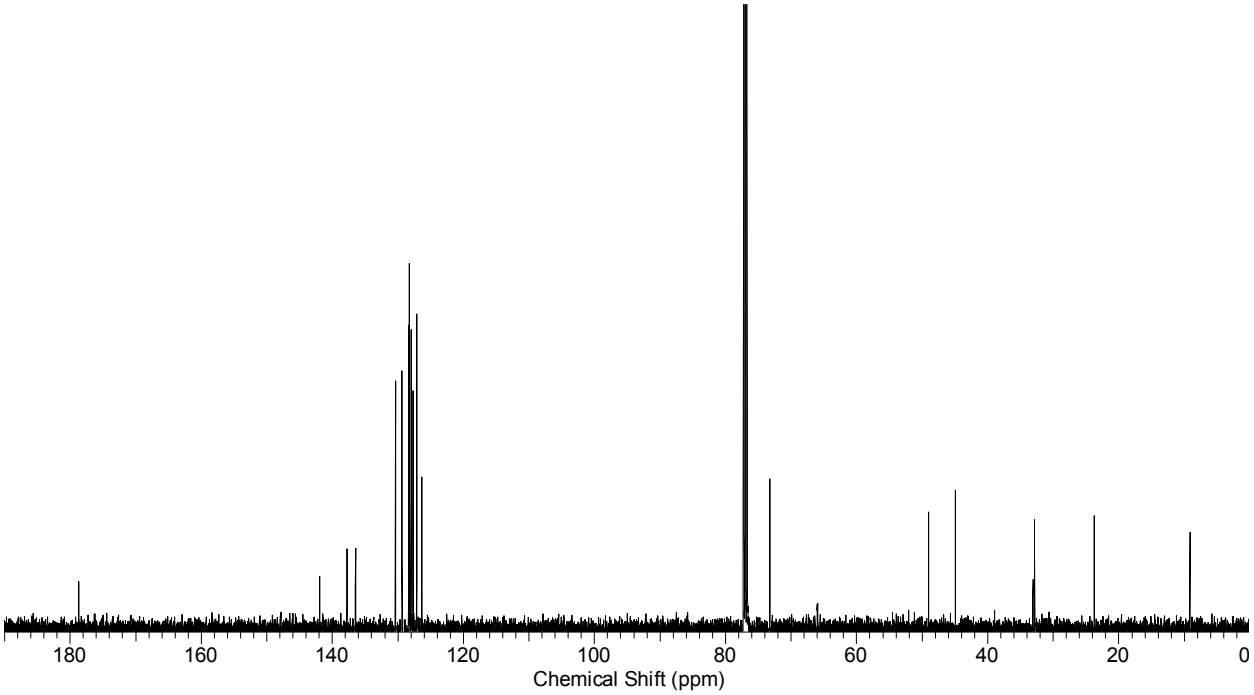
122

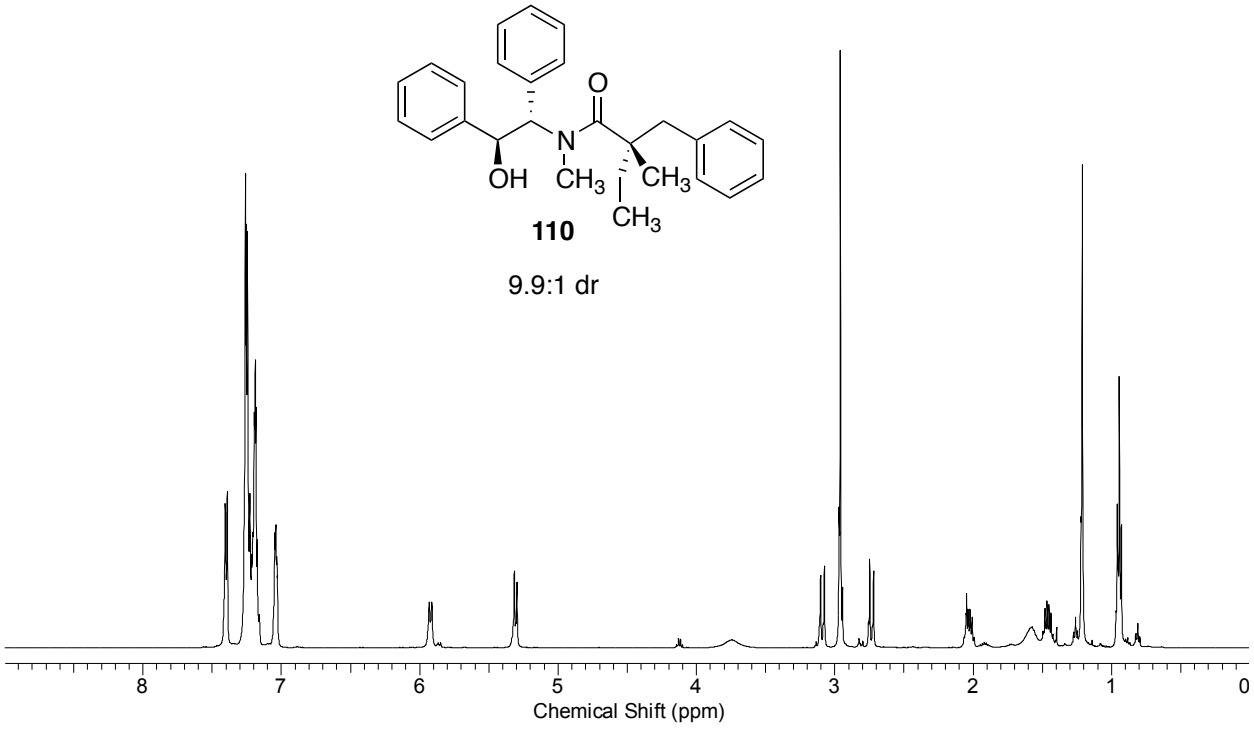

O
N
OH
CH3
CH3
CH3

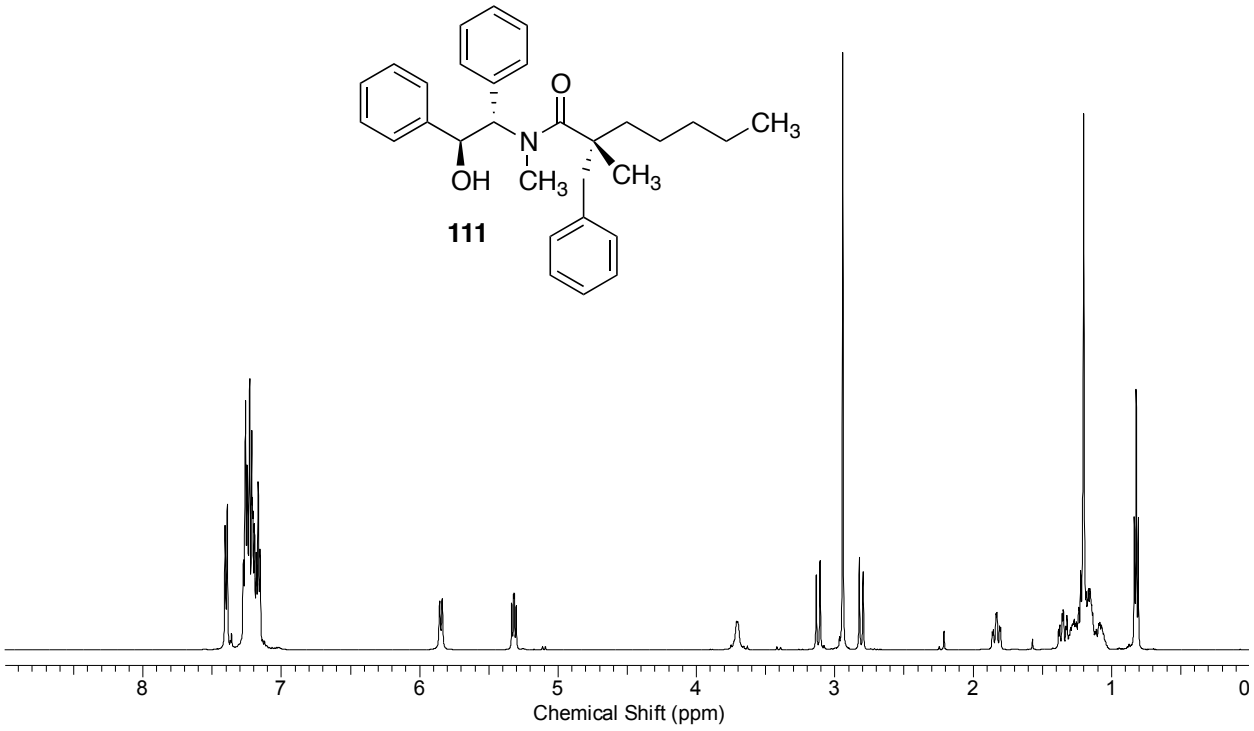
110

≥19:1 dr

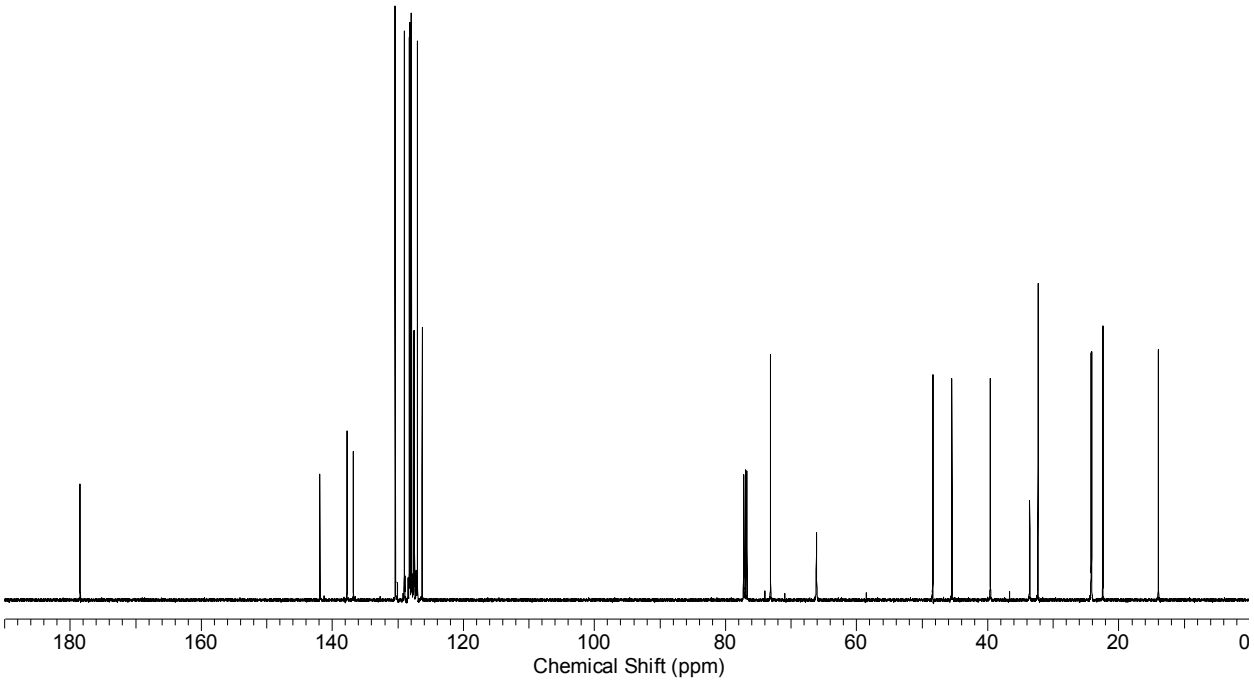
8
7
6
5
4
3
2
1
0
Chemical Shift (ppm)

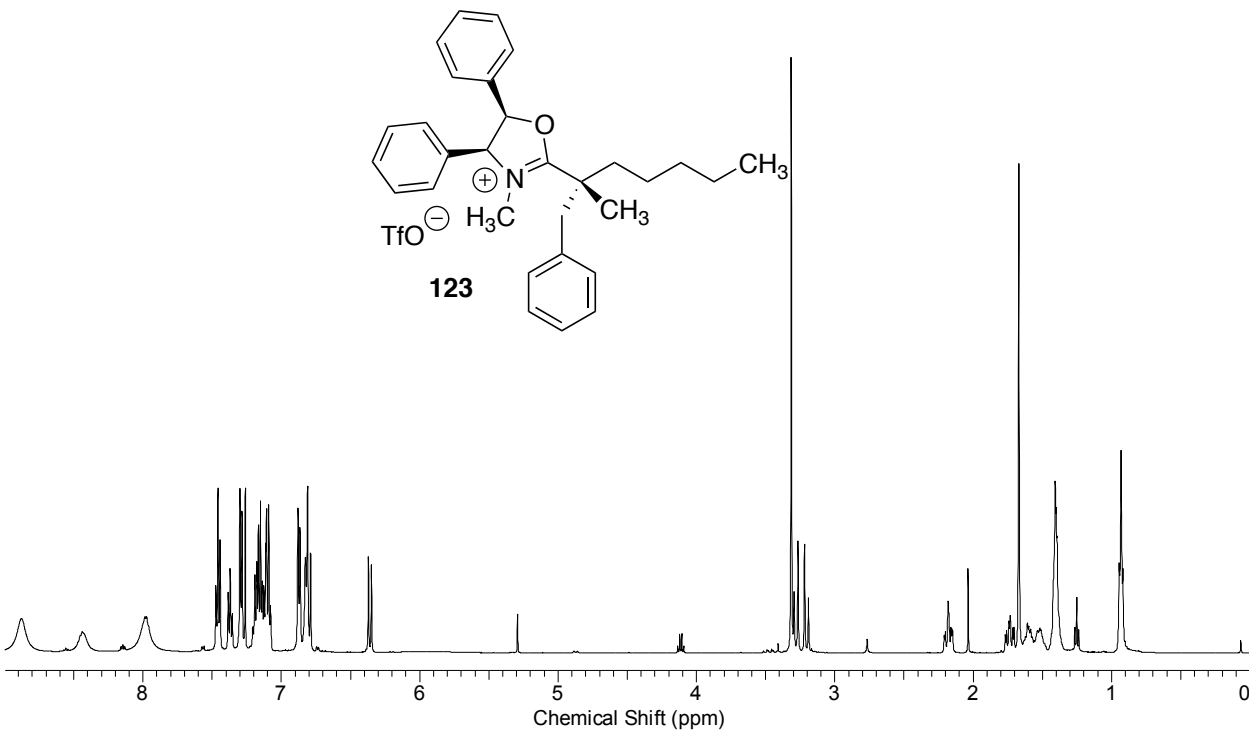

180
160
140
120
100
80
60
40
20
0
Chemical Shift (ppm)


O
N
OH
CH3
CH3
CH3
110
9.9:1 dr
8
7
6
5
4
3
2
1
0
Chemical Shift (ppm)

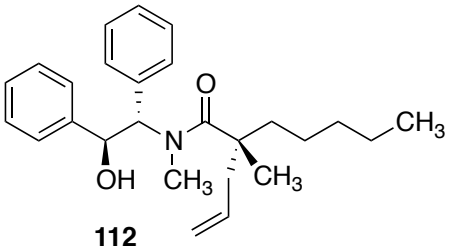

O
CH3
N
OH
CH3
CH3
8
7
6
5
4
3
2
1
0
Chemical Shift (ppm)

111


180
160
140
120
100
80
60
40
20
0
Chemical Shift (ppm)

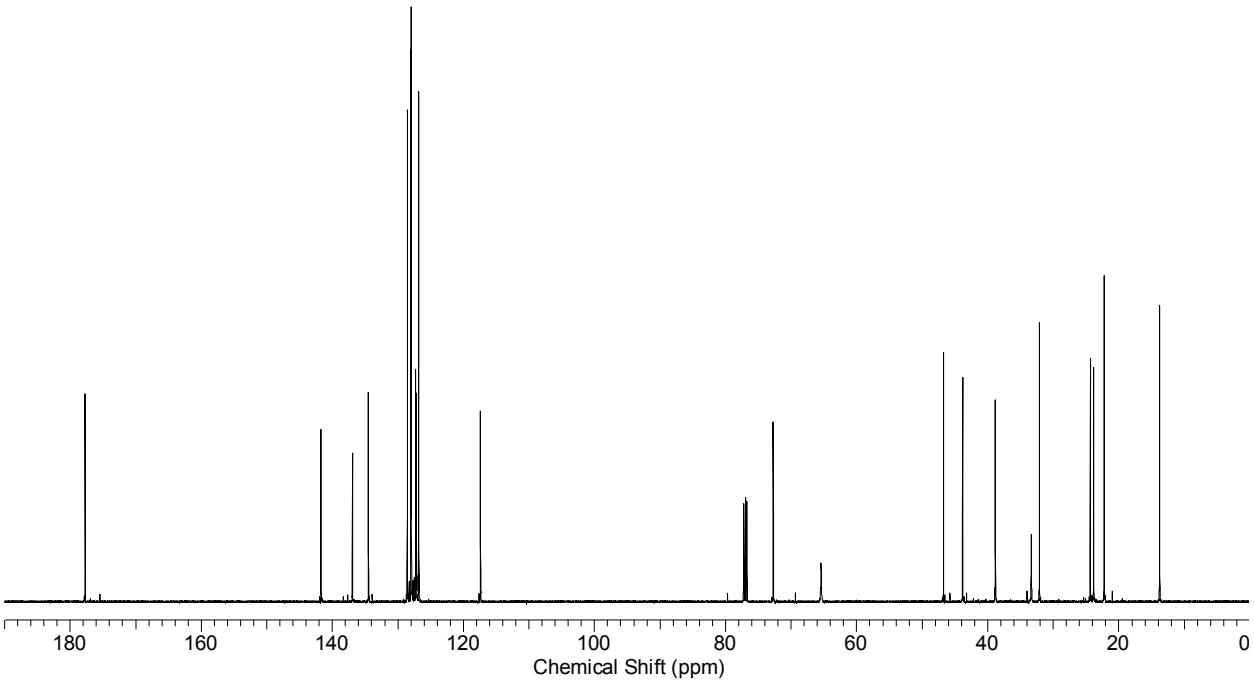


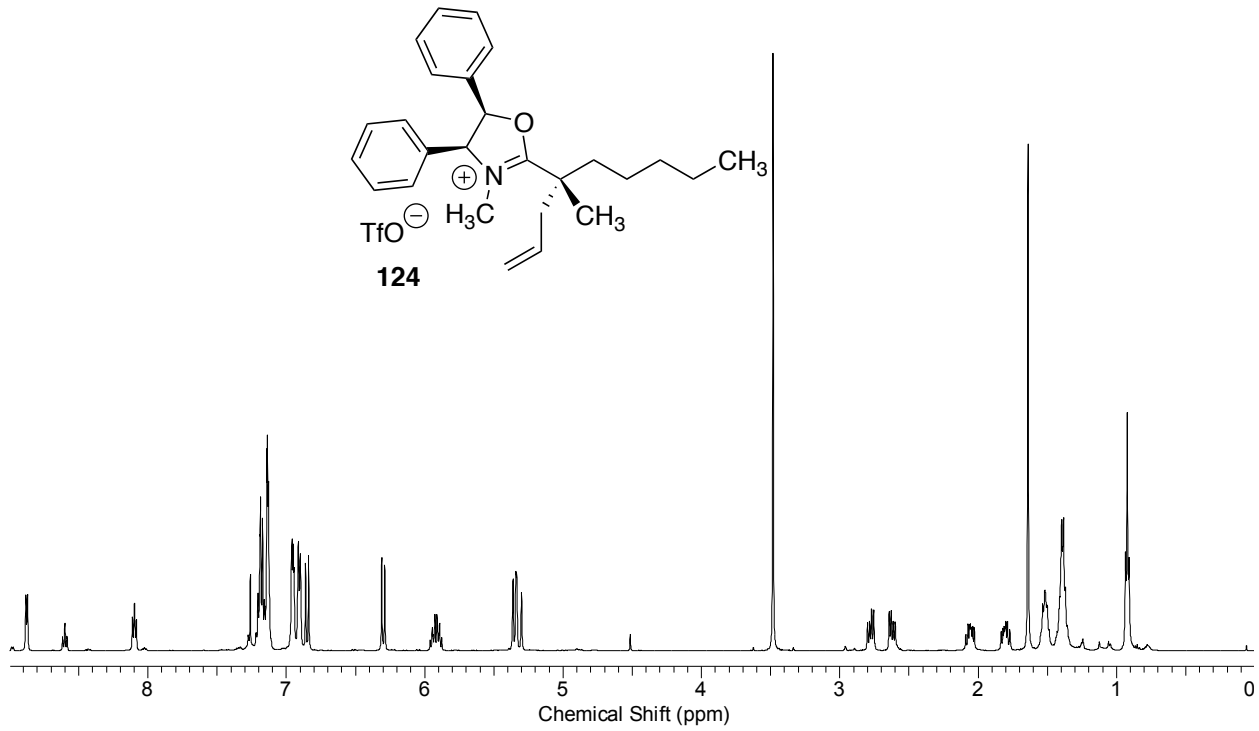
123


O
N
CH3
OH
CH3
CH3

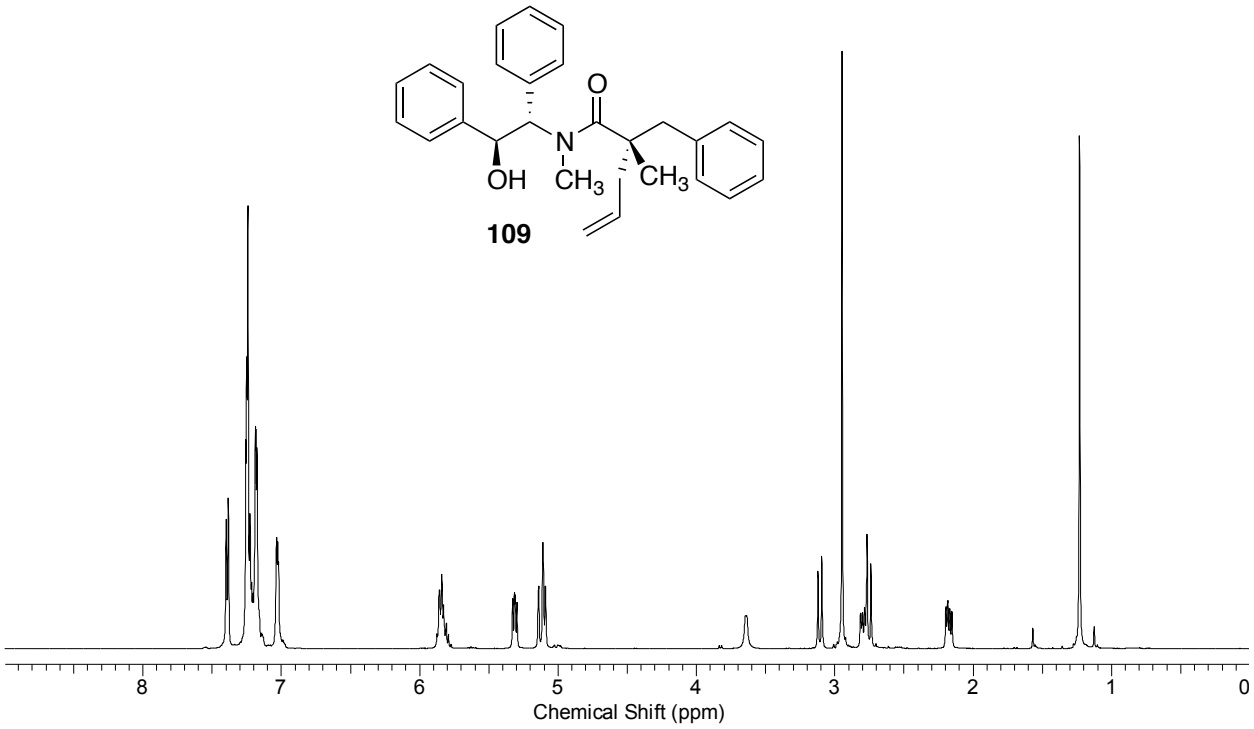
112

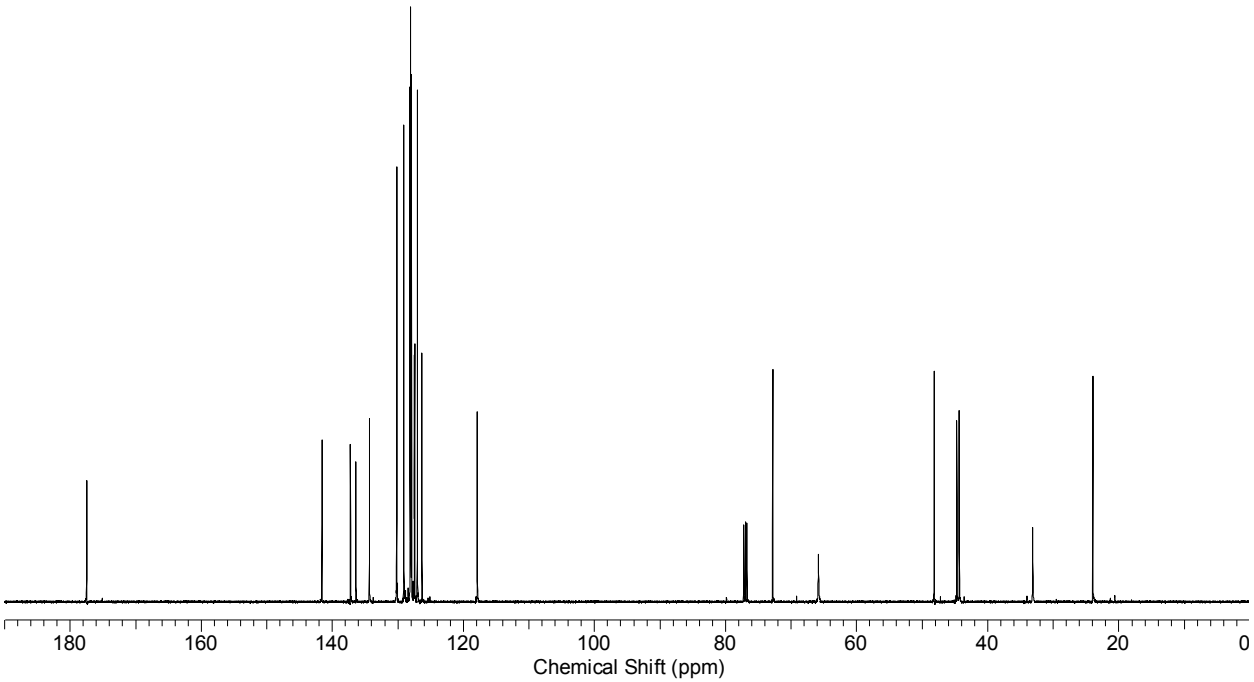
8
7
6
5
4
3
2
1
0
Chemical Shift (ppm)

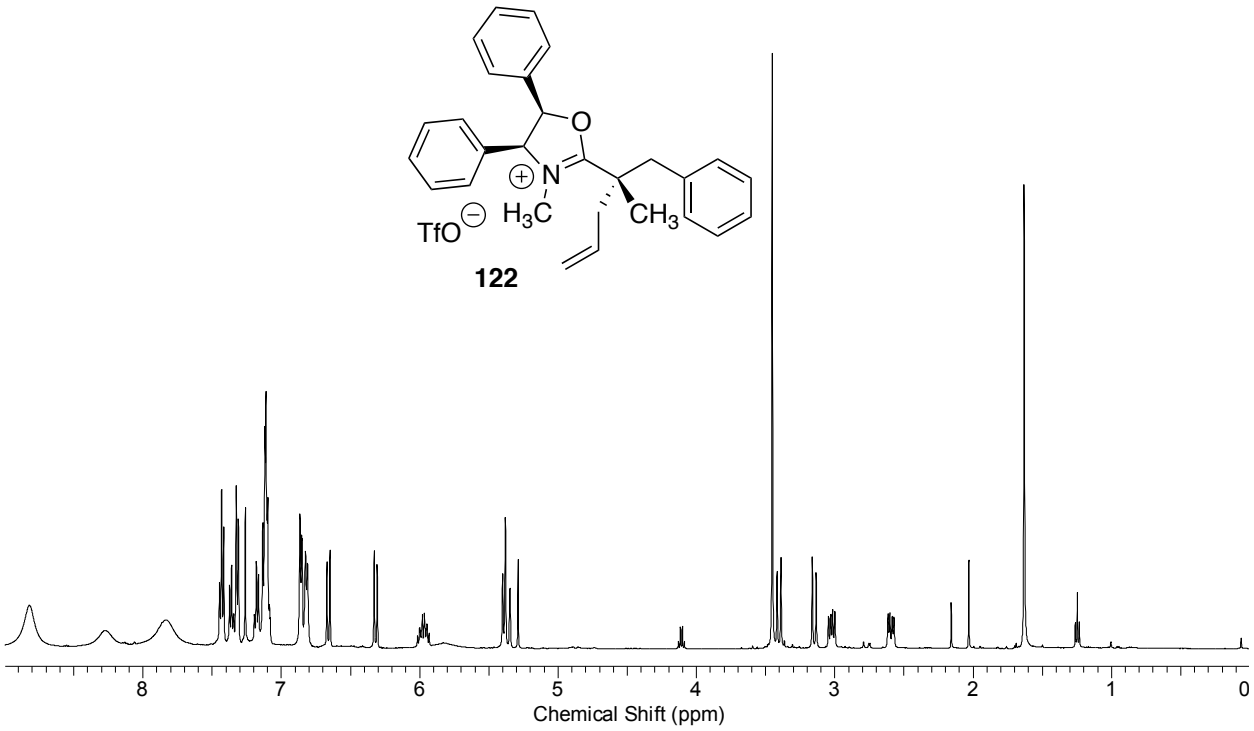

180
160
140
120
100
80
60
40
20
0
Chemical Shift (ppm)



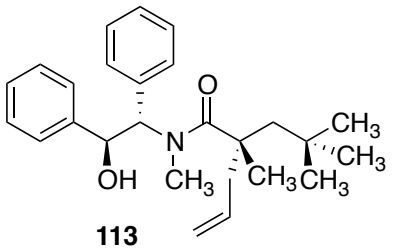
124


O
N
OH
CH3
CH3
109
8
7
6
5
4
3
2
1
0
Chemical Shift (ppm)


180
160
140
120
100
80
60
40
20
0
Chemical Shift (ppm)

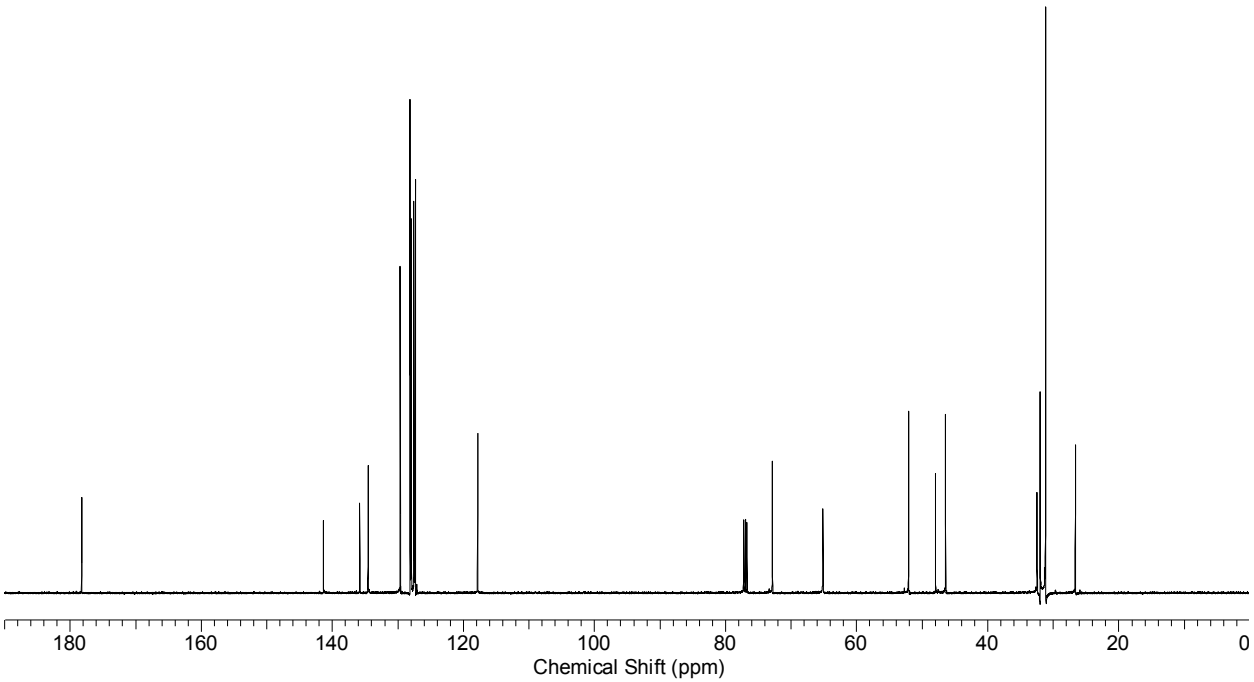


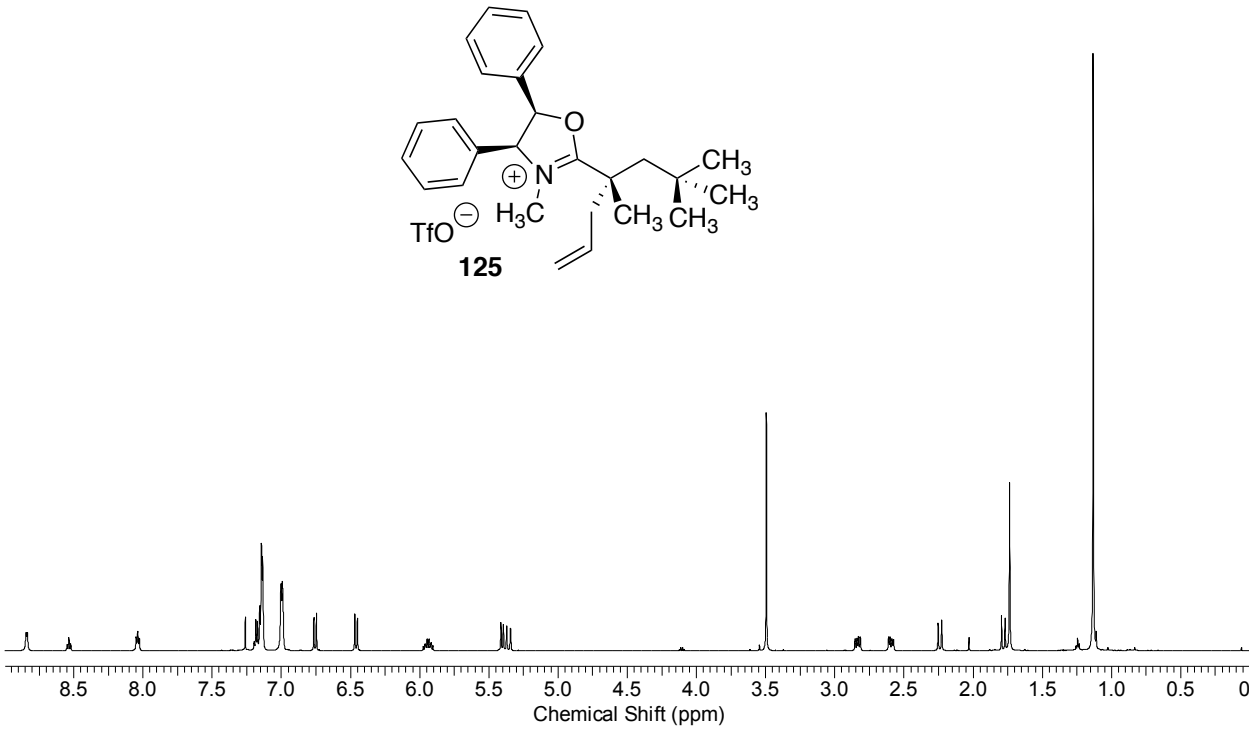
122

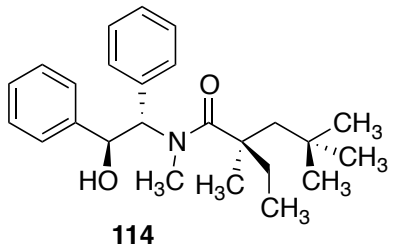

O
N
CH3
CH3
CH3
CH3
CH3
OH
CH3

113

8
7
6
5
4
3
2
1
0
Chemical Shift (ppm)

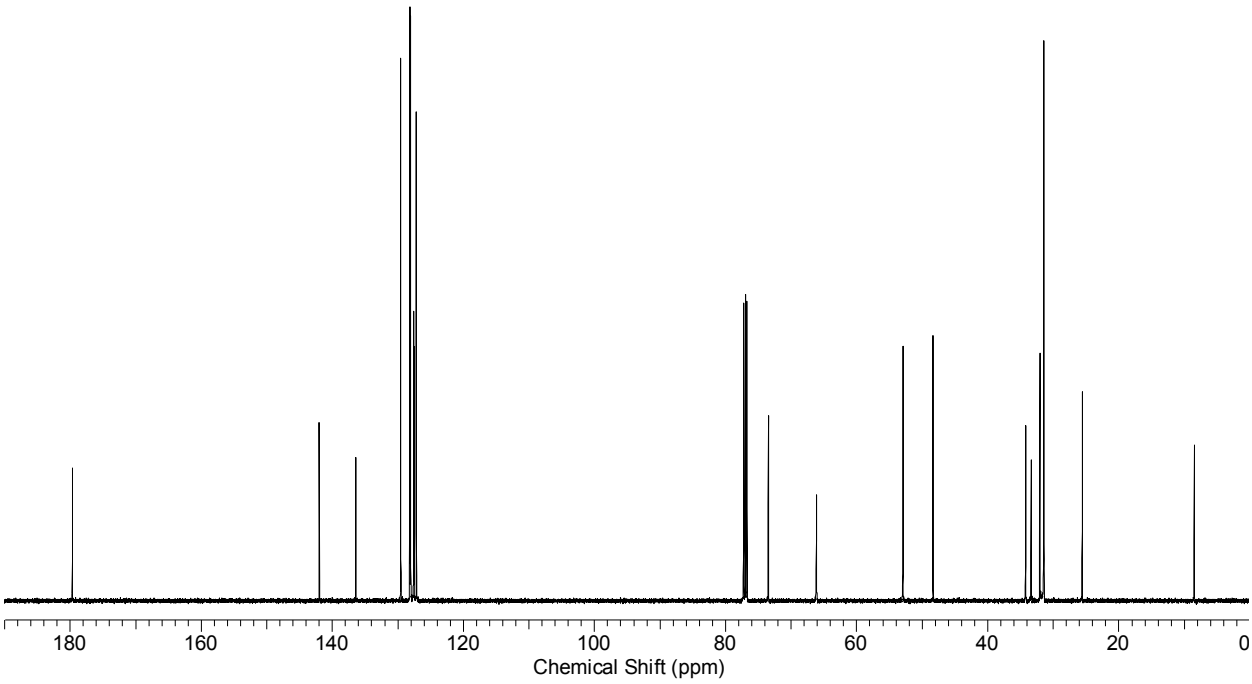

180
160
140
120
100
80
60
40
20
0
Chemical Shift (ppm)

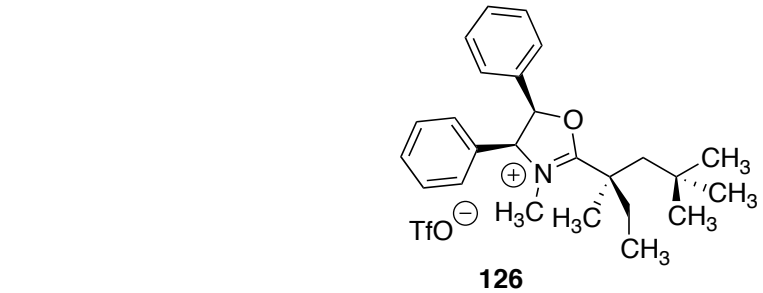

O
N
H3C
CH3
CH3
CH3
CH3
TfO
125
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0
Chemical Shift (ppm)


O
N
HO
H_3C
H_3C
CH_3
CH_3
CH_3
CH_3

114

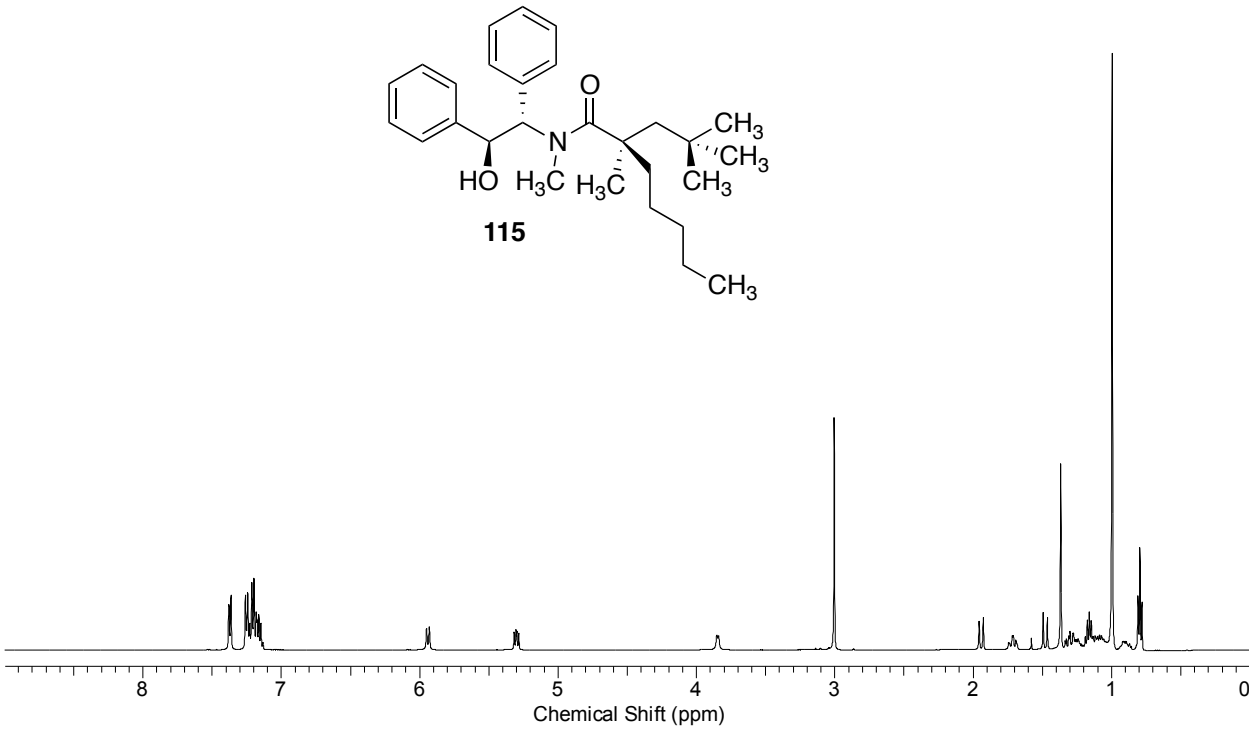
8
7
6
5
4
3
2
1
0
Chemical Shift (ppm)


180
160
140
120
100
80
60
40
20
0
Chemical Shift (ppm)

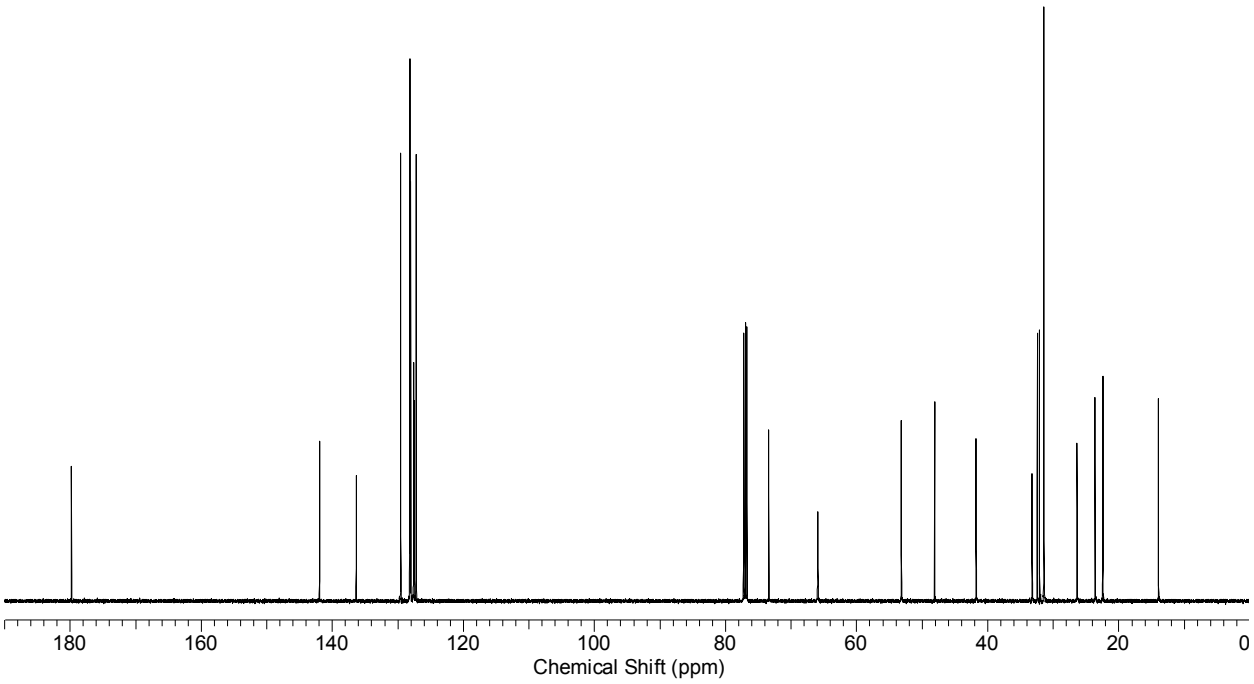

O
N
CH3
CH3
CH3
H3C
H3C
TfO
CH3

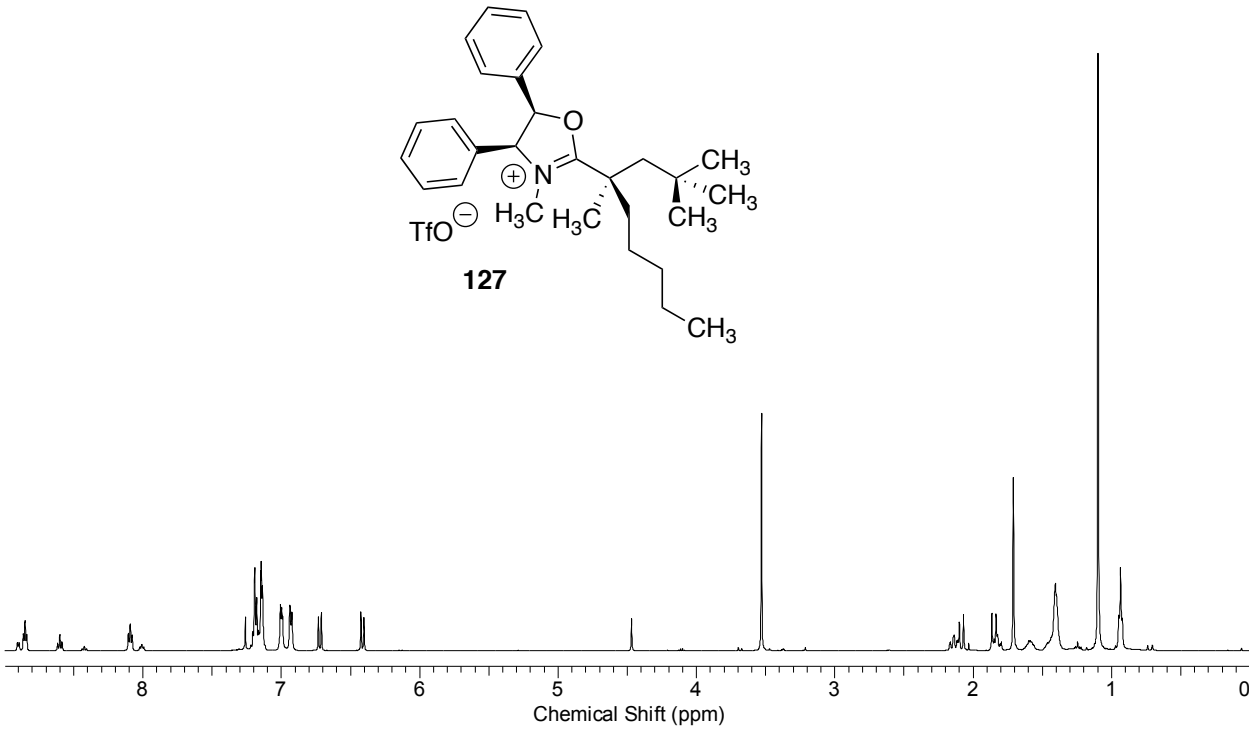
126

8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0
Chemical Shift (ppm)


O
N
HO
H_3C
H_3C
CH_3
CH_3
CH_3
CH_3
8
7
6
5
4
3
2
1
0
Chemical Shift (ppm)

115


180
160
140
120
100
80
60
40
20
0
Chemical Shift (ppm)



127